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Original Communications

CARCINOMA SUBSEQUENT TO THE RADIOTHERAPEUTIC MENOPAUSE*

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IN THE routine follow-up examination of about 1,100 patients in whom an artificial menopause had been induced because of benign uterine bleeding, fibromyoma, or one of a few other benign conditions, there were noted 36 cancers in various parts of the body, 15 of which were of the uterus (9 in the corpus and 6 in the cervix). This may not appear to be a large number of cases in view of the fact that some of the patients were under observation for as long as twenty-five years. However, the data seemed sufficient to warrant a thorough statistical analysis. The results of this analysis showed that there was a slight excess of cancer other than uterine and a statistically significant excess of cancer of the uterus, particularly of the corpus, over the number that might be expected to occur among an equivalent group of the general population followed for the same length of time.

Similar series of patients have been reported and discussed by Werner,¹ Vogt,² Burnam,³ Norris and Behney,⁴ Schmitz,⁵ Strachan,⁶ Luker,⁷ Costolow,⁸ Scheffey⁹ and Macfarlane.¹⁰ The observed cases of carcinoma in the different series amounted to from 0.3 to 1.46 per cent of the patients originally treated by the artificial menopause. However, the validity of these percentages cannot be assessed generally because the number of patients followed is not stated. Furthermore, these percentages cannot be interpreted safely as incidence figures,

*Read at a meeting of the New York Obstetrical Society, Feb. 8, 1944.

since the duration of the follow-up is not given, except in the case of Burnham,³ who found an incidence of 1.46 per cent for cancer of the uterus among 625 patients followed for ten or more years.

Since it is important to determine whether the threat of carcinoma is sufficient to influence the management of these benign cases, an accurate estimate of the probability of such a patient subsequently contracting carcinoma should be made. This has been made possible by the records of 1,108 patients of whom 958 were followed for an average of 6.7 years each, giving an aggregate experience of 6,402 person-years, which would seem entirely adequate for an extended statistical analysis.

TABLE I. LENGTH OF FOLLOW-UP OF PATIENTS IRRADIATED FOR BENIGN UTERINE CONDITIONS AND CARCINOMAS DEVELOPING DURING THIS FOLLOW-UP

AGE WHEN TREATED	DURATION OF FOLLOW-UP									TOTAL CASES WITH FOLLOW-UP	LENGTH OF FOLLOW-UP (YEARS)		NUMBER OF CARCINOMAS	
	0 YR.	UNDER 1 YR.	1-2 YR.	2-4 YR.	5-9 YR.	10-14 YR.	15-19 YR.	20-24 YR.	25-29 YR.		TOTAL	AVERAGE	ALL KINDS	UTERINE
Below 25	2	1	2	3	3	1	2	2	0	14	129.0	9.2		
25-29	3	3	0	3	5	4	0	1	0	16	122.0	7.6		
30-34	5	4	2	10	14	6	1	1	0	38	260.0	6.8	1	
35-39	24	9	14	25	44	17	5	4	1	119	860.5	7.2	2	
40-44	49	21	41	81	86	41	18	6	0	294	1,963.0	6.7	12	7
45-49	39	33	40	87	90	53	13	5	1	322	2,086.0	6.5	14	5
50-54	26	14	22	30	38	15	5	3	0	127	772.5	6.1	6	3
Over 55	2	1	2	8	11	4	0	2	0	28	209.0	7.5	1	
Total	150	86	123	247	291	141	44	24	2	958	6,402.0	6.68	36	15

TABLE II. CASES OF NONUTERINE CARCINOMA SUBSEQUENT TO RADIATION THERAPY FOR BENIGN UTERINE CONDITIONS

CASE NO.	SITE	AGE WHEN TREATED	YEARS AFTER TREATMENT WHEN CANCER OCCURRED	YEARS OF FOLLOW-UP
1	Ovary	49	9	10
2	Ovary	48	6/12	6/12
3	Stomach	49	9	10
4	Thyroid	39	1	5
5	Rectum	44	3/12	4/12
6	Rectum	35	8	8
7	Rectum	45	9	9
8	Bladder	40	20	20
9	Bladder	50	13	24
10	Breast	45	5	28
11	Breast	44	3	7
12	Breast	50	10	16
13	Breast	43	8	8
14	Breast	56	5	24
15	Breast	46	14	14
16	Breast	46	7/12	7/12
17	Breast	48	5	5
18	Breast	51	1	2
19	Sigmoid	44	10	12
20	Sigmoid	34	13	13

The fundamental data on which this study is based are given in Tables I, II, and III. Table I gives the distribution of the 1,108 patients with respect to age at entry into the study, and length of follow-up. It will be noted that practically all of the patients entered between the ages of 30 and 55 years. The subsequent analysis relates only to the 958 patients who were actually followed. While the 150 patients without follow-up may be a selected part of the whole,

TABLE III. TABULATION OF PRINCIPAL CLINICAL ASPECTS OF CASES OF UTERINE CARCINOMA SUBSEQUENT TO RADIATION FOR BENIGN CONDITIONS

CASE NO.	AGE (YR.)	ORIGINAL TREATMENT				CARCINOMA					
		INDICATIONS AND SIZE OF UTERUS	CURETTINGS BIOPSY	TREATMENT	ONSET OF AMENORRHEA	OC-CURRED AFTER TREATMENT (YR.)	DURATION OF BLEEDING	OPER. FINDINGS	MICROSCOPIC	TREATMENT	RESULT
Cases of Carcinoma of Corpus											
1	43	Bleeding Ut. 4 mo.	Endometrium Normal	D. & C. Ra.	1 mo.	9	2 wk.	Extensive ca.	Adeno-ca.	Hyst. & X-ray	D. 2 yr. Ca.
2	46	Bleeding	0	X-ray		10	3 mo.		Adeno-ca.	Hyst.	D. 10 yr. Tbc.
3	51	Bleeding Ut. 6 wk.	Cyst. & Gl. Hyperplasia	D. & C. Ra.	2 mo.	4	3 wk.		Adeno-ca.	Hyst.	A.W. 9 yr.
4	48	Bleeding Ut. 2 mo.	Mod. Gl. Hyperplasia	D. & C. Ra.	Cont. 3 mo. X-ray	21	?	Adeno-ca.	Ra.		D. 1 yr. Ca.
5	40	Bleeding	Cyst. & Gl. Hyperplasia	D. & C. Plastic	1 mo.	9	?	Adeno-ca.	Hyst.		A.W. 6 yr.
6	50	Bleeding Ut. 2 mo.	0	X-ray	1 mo.	10	10 days	Adeno-ca.	Ra. & hyst.		A.W. 4 yr.
7	49	Bleeding Ut. 4 mo.	0	X-ray	1 mo.	9	1 mo.	Adeno-ca.	Ra. & hyst.		A.W. 4 yr.
8	43	Bleeding	Cyst. & Gl. Hyperplasia	Plastic D. & C. X-ray	Immediate	2	1 mo.	Adeno-ca.	Ra. & hyst.		A.W. 5 yr.
9	49	Bleeding	?	D. & C. Ra.	Immediate	13	?	Adeno-sarcoma	Hyst.		D. 2 yr. Ca.
Cases of Carcinoma of Cervix											
10	44	Bleeding Ut. 5 mo.	Curettings none	X-ray	3 mo.	8	3 wk.	Endo-cervix	Adeno-ca.	D. & C. Ra.	D. 2 yr. Ca.
11	45	Bleeding	No curettings	D. & C. Ra.	Immediate	6	1 yr. & 2 wk.	Endo-cervix	Adeno-ca.	D. & C. Ra.	D. 4 yr. Ca.
12	41	Bleeding Ut. 3 mo.	Normal secretory	D. & C. Ra.	1 mo.	18	1 mo.	Cervix	Squamous	X-ray D. & C. Ra.	Alive with Ca. 9 mo.
13	40	Bleeding Ut. 2 mo.	Mod. gland. Hyperplasia	D. & C. Ra.	Immediate	12	6 mo.	Endo-cervix	Squamous	D. & C. Ra.	A.W. 4 yr.
14	51	Bleeding Ut. 4 mo.	Normal proliferative	D. & C. Ra.	Immediate	7	?	?	Squamous	?	D. 2 yr. Ca.
15	42	Bleeding	Normal proliferative	D. & C. Ra.	1 mo.	12	2 mo.	Endo-cervix	Squamous	D. & C. Ra. X-ray	A.W. 2 yr.

Key: Size of uterus is compared with the pregnant uterus. Cyst. = cystic; Gl. = glandular; D. = dilatation and curettage; Cont. = continued; Hyst. = hysterectomy; D. = died; A. W. = alive and well.

such possible selection should not influence greatly the generality of the results, in view of the relatively small size of this group. Table I also gives the number of carcinomas developing among the patients according to their age at entry. The more detailed classification of the 36 carcinomas as to the site, age of the patient, and length of follow-up is given in Tables II and III.

Before undertaking the detailed analysis of the data given in Table I, we shall first present some preliminary calculations concerning the general population. In the first place, we may inquire as to the proportion of females in the general population between the ages of 30 and 55 who will survive to the age of 80. According to the annual mortality rates from all causes at the various ages prevailing among females in the United States in 1930, it may be deduced by the usual actuarial procedures¹¹ that some 26 to 31 per cent of women between the ages of 30 and 55 will survive to the age of 80.

Second, we may inquire as to the proportion of these females in the general population in the age group 30 to 55 who would contract cancer by the age of 80. This proportion can be determined by following through such a group of individuals, subjecting the survivors year after year to the appropriate annual incidence rates of cancer at the various ages. Since we do not know the annual incidence rates of cancer at the various ages, because cancer is not generally a reportable disease, we shall have to use the annual mortality rates, modifying these, if possible, to reflect incidence more clearly. For this purpose it was assumed that the incidence rate in any age group could be taken approximately as the mortality rate among individuals five years older. Thus the individuals between the ages of 35 and 40 are regarded as subjected to the risk expressed by the annual mortality rate pertaining to individuals between the ages of 40 and 45. As a result of this modification, our estimate of the probability of contracting cancer is about 20 per cent higher than it would be if death rates were employed directly as incidence rates. It might be argued that this modification assumes that a case of cancer survives some five years on the average. While this average may be exaggerated, any such exaggeration will leave a margin for the fact that not all cases of cancer terminate fatally. Applying the mortality rates, as given in Table IV¹¹⁻¹³ in the manner described above, to a group of females in the general population between the ages of 30 and 55 followed year by year until the age of 80, it follows that some 15 per cent will have had cancer by the age of 80, and some 2.8 per cent cancer of the uterus.

Thus, among our 958 patients, all of whom were essentially between 30 and 55 years, we might accordingly expect some 15 per cent, or 144, to develop cancer, and some 26, cancer of the uterus, if they were comparable to the general population and were all followed to the age of 80. However, since the 958 patients here studied were followed for only 6.7 years on the average and not until the age of 80, it is obvious that the numbers 144 and 26 cannot be used as the normal expectancy. We shall have to employ some modification of the above procedure in order to determine the number of cancers which would be expected among a group of 958 females in the general population distributed by age and followed up as are those of Table I.

TABLE IV. DEATH RATES PER 100,000 FEMALES FROM CANCER AND OTHER MALIGNANT TUMORS, AND FROM CANCER OF THE UTERUS, UNITED STATES, 1930

AGE (YEARS)	CANCER AND OTHER MALIGNANT TUMORS	CANCER OF UTERUS
25-29	13.8	5.1
30-34	32.0	12.7
35-39	58.4	21.0
40-44	113.3	40.7
45-49	172.1	54.2
50-54	249.2	69.6
55-59	356.2	87.2
60-64	458.7	92.4
65-69	595.5	102.0
70-74	803.4	114.7
75-79	948.2	110.8
80-84	1111.2	125.3

TABLE V. DETERMINATION OF FOLLOW-UP IN TERMS OF PERSON-YEARS FOR THE 294 PATIENTS ENTERING AT AGE 40, AND THE EXPECTED CASES OF CANCER

(1) AGE AT TREATMENT	(2) NUMBER REMAIN- ING IN THE STUDY	(3) NUMBER WITH- DRAWN FROM OBSERVATION	(4) PERSON-YEARS OF OBSERVATION IN THE AGE GROUP	(5) EXPECTED CASES* OF CANCER
40	294	21	283.5	0.5
41	273	41	252.5	0.4
42	232	81	574.5	1.0
45	151	86	540.0	1.4
50	65	41	222.5	0.8
55	24	18	75.0	0.3
60	6	6	15.0	0.1
65	0	0		
Total			1963.0	4.5

*Applying to column (4) the mortality rates of Table IV pertaining to persons in the age group older by 5 years.

We may illustrate the procedure employed by following through the calculations for the 294 patients entering in the 40 to 45 age group. As seen in Table I, these were followed for a total of 1,963 years or 6.7 years on the average. Each of the 1,963 years is the equivalent of one person followed for one year and represents a unit of exposure to the risk of contracting cancer expressed by the annual incidence rate. We shall follow the customary practice of denominating this unit a "person-year." In order to determine properly the number of cases of cancer to be expected among these 1,963 person-years, it is necessary to distribute them by age, since the risk of contracting cancer varies with age. The method of simultaneously calculating the exposure and distributing it by age is analogous to that utilized by insurance companies and is illustrated in Table V for these 294 patients. For simplicity, they are all regarded as entering the study at the age of 40 years. Beginning with 294 patients 40 years of age, we note from Table I that 21 have left the study before the end of the first year, so that there are only 273 remaining at the age of 41 years. Of these, 41 withdrew before the end of the second year, leaving 232 at 42 years of age, and so on, until there are no patients left by the age of 65 years. The number of person-years is then calculated for each age group. For example, in the 45 to 50 group, of the 151 present at the age of 45 years, 86 are lost from observation and only 65 remain by 50 years of age. These 65 must be credited

with 5 years of exposure each in this age group—that is, 325 person-years in all. The 86 lost from observation are assumed to be withdrawn uniformly throughout this period, being credited with $2\frac{1}{2}$ years each, on the average, that is, 215 person-years in all. The total number of person-years between the ages 45 and 50 is thus 325 plus 215, or 540. The exposure in the remaining age groups was calculated similarly. Multiplying the person-years in each age group by the appropriate death rates modified as previously indicated, we obtain 4.5 as the expected number of cases of all cancers among the 294 patients, contrasted with the observed number of 12 cases. Similarly multiplying by the death rates for cancer of the uterus, we find 1.3 expected cases, as compared to the observed number of 7.

TABLE VI. AGE DISTRIBUTION OF 6,402 PERSON-YEARS ACCUMULATED BY 958 PATIENTS FOLLOWED UP FOR VARYING PERIODS AS GIVEN IN TABLE I

AGE	PERSON-YEARS
20-24	54.0
25-29	94.5
30-34	210.0
35-39	573.0
40-44	1,390.5
45-49	1,833.5
50-54	1,297.5
55-59	644.0
60-64	215.0
65-69	65.0
70-74	20.0
75-79	5.0
Total	6,402.0

By the same procedure as that just employed for the 294 patients entering at the age of 40 years, the exposure of each group of patients was calculated and distributed according to age. For this purpose, the 14 patients under the age of 25 years and the 28 patients over 55 years were regarded as entering at the ages of 20 and 55 years, respectively. The age distribution of the total 6,402 person-years, obtained by summing the various tables similar to Table V, is given in Table VI. Multiplying the person-years by the appropriate death rates, we find that there should be 17.4 cancers, of which 4.4 should be cancer of the uterus. The observed number of cancers, 36, of which 15 are of the uterus, is far in excess of the expected number, the difference being statistically significant. This seems largely accounted for by the excess of uterine cancers, which is very significant, the ratio of the observed cases to the normal expectancy being 3.4. In fact, the incidence of cancer other than uterine does not seem unduly large, the observed number being 21 and the expected 13. This will be discussed below in more detail.*

The observed and expected cases of cancer for each age group at entry into the study are separately portrayed in Table VII, showing that the excess is

*It should be noted that the follow-up data as given in Table I and as further shown in Table VI includes the follow-up on the 36 patients after they contracted cancer. It might properly be argued that this latter follow-up is biased. However, the follow-up on the 36 patients after contracting cancer is negligible, amounting to only 127 person-years, as may be observed from Tables II and III. Since this constitutes only 2 per cent of the total follow-up, the extra refinement of subtracting these 127 person-years in the appropriate age groups in Table VI was not deemed necessary.

TABLE VII. OBSERVED AND EXPECTED CASES OF CANCER BY AGE AT ENTRY OF PATIENT INTO THE STUDY

AGE		UNDER 25	25-29	30-34	35-39	40-44	45-49	50-54	OVER 55	TOTAL
All Cancer	Observed cases	0	0	1	2	12	14	6	1	36
	Expected cases	0.1	0.1	0.2	1.4	4.5	6.6	3.3	1.2	17.4
Uterine Cancer	Observed cases	0	0	0	0	7	5	3	0	15
	Expected cases	0.0	0.0	0.1	0.4	1.3	1.7	0.7	0.2	4.4

consistently present in all the age groups in which there was an appreciable number of patients.

We conclude from the statistical analysis that, in patients selected as were ours, subsequent to the radiotherapeutic menopause for excessive uterine bleeding, fibromyoma of the uterus, or for other benign conditions, carcinoma of the uterus occurs some 3.4 times as frequently as in the general population. Since some 2.8 per cent of women in the general population between the ages of 30 and 55 years will contract carcinoma of the uterus by the age of 80 years, we might conclude that 3.4 times 2.8 per cent, or 9.6 per cent, of the group here followed will be similarly afflicted.

There is not a corresponding excess of cancers in other organs. While 21 of these were observed instead of an expected 13, five were discovered within one year of the first observation and according to the prevailing custom would be considered coincident with and not subsequent to the original contact, leaving 16 which were properly subsequent to the original procedure, an excess statistically not significant. We shall discuss these cases no further except to point out with proper humility that a specialist treating women of this age group must accept the responsibility for a complete diagnosis before instituting any form of therapy. We shall hereafter confine our discussion to the uterine carcinomas.

While a statistical analysis has been justified in view of the mass of data, we must examine the reliability and validity of the original observations and of some of the assumptions made in the analysis.

The employment of the mortality rates as incidence rates is subject to two possible errors. The reliability of the mortality rates has been studied by MacDonald,¹⁴ who finds an error of understatement in the reporting of carcinomas of some 6 per cent, the error being greatest for the inaccessible growths. That the error is greater than this is suggested by Pohlen and Emerson,¹⁵ who, in a comparison of clinical diagnosis with autopsy findings, found that the clinical topographical and etiological diagnosis was correct in only 65 per cent of the cases of carcinoma of the corpus and in 86 per cent of the carcinomas of the cervix. In addition, since cancer is not generally a reportable disease, there are very little data from which to study its incidence. It was necessary, therefore, to employ mortality rates as a basis for calculation. Because of the high fatality rates, these have been assumed¹⁶ to give a reasonably good picture of incidence also. Against this assumption, we know that a respectable number of patients treated for cancer of the uterus survive for five or more years. In New York State, where cancer has been a reportable disease since 1940, there were reported, in 1942, 1,330 new cases of cancer of the uterus,¹⁷ while in that

same year only 905 deaths were recorded, giving an excess of living new cases over deaths of 47 per cent, more than double our correction of 20 per cent. The "new" cases, however, probably include cases which had existed prior to 1942 but were not reported and may not indicate the actual incidence. It is quite likely that our correction is a conservative one.

Regardless of the incidence figures used as a basis of calculation, the estimate 9.6 per cent already given as the probability of contracting cancer of the uterus by the age of 80 years among women similar to the ones here studied will be essentially correct. This is due to the fact that any change effected in the estimate of 2.8 per cent for the normal probability by the choice of different incidence rates would be accompanied by a compensatory change in the ratio 3.4 which the observed 15 cases of cancer of the uterus bear to the normal expectancy.

The question may be raised as to whether these cancers were truly "subsequent" to the original procedure or whether they were present at the original treatment and overlooked, remaining quiescent for a number of years and possibly even being inhibited by the sterilizing dose of radiation.* It is customary in considering cancer of the cervical stump to consider cases revealed within two years and by some, three years, as having been present when the hysterectomy was performed. Applying this rule to the six cases of cancer of the cervix here presented, all of them would be classified as "subsequent" since the shortest interval was six years.

Cancer of the corpus may lie quiescent for a longer time and the determination of whether or not it was coincident with the original treatment is more difficult. In the cases here reported the intervals were 2, 4, 9, 9, 9, 10, 10, 13, and 21 years, respectively. The patient with the two-year interval (Case 8, Table III) was treated at the age of 43 by a complete vaginal plastic. Because of moderately excessive menstruation she was given an x-ray menopause. The curettage performed by the "fractional" technique yielded normal appearing endometrium which was diagnosed microscopically as cystic and glandular hyperplasia. The periods stopped immediately. Two years later curettage for recurrent bleeding revealed a diffuse, apparently superficial adenocarcinoma. This case is entered as "subsequent" because it was handled throughout by one of us. The curettage was meticulous and if a carcinoma was overlooked, it was too small to be revealed in the curettings. Furthermore, the x-ray dose of 400 roentgens to the uterus is insufficient to affect an adenocarcinoma.

The patient with the four-year interval, Case 3, was treated by intrauterine radium (1,800 mg. hr.) for uterine bleeding from a slightly enlarged uterus. Curettage yielded a polyp and endometrium showing cystic and glandular hyperplasia. Four years later curettage for recurrent uterine bleeding yielded a single bit of tissue 4 mm. in diameter, an adenocarcinoma. The uterus removed six weeks after a dose of 2,400 mg. hr. of radium showed no carcinoma. There may have been a malignant transformation of a polyp. If so, it was not apparent in the original specimen.

*We are here concerned only with the question of the validity of the data and not with the important problem of proper diagnosis in these cases, which has been ably discussed by Scheffey.⁹

Three cases were treated by x-ray without a curettage; one because of active pulmonary tuberculosis and two for personal reasons on the part of the patient, the decision to forego the curettage being shared, however, by the physician. In the tuberculous patient, Case 2, slight vaginal bleeding persisted for a year and suggested some organic lesion. The carcinoma appeared after an interval of ten years. Bleeding in the other two women, Cases 6 and 7, ceased promptly. The carcinoma appeared after nine and ten years, respectively. While the long interval suggests that the carcinoma was not present originally, its appearance at any time emphasizes the responsibility undertaken by the physician when a diagnostic curettage is not performed.

Inhibition of a cancer by intrauterine radium seems unlikely in these cases except possibly in Case 3 in which the carcinoma appeared four years after the original treatment. Among cases treated in our clinic for frank carcinoma of the corpus by intrauterine radium in doses of from 2,400 to 8,000 mg. hr. combined with x-ray therapy, in only one case was there a local recurrence of the carcinoma after three years. Since the shortest interval in our series of cases was nine years, with the exception of the cases above described, it seems improbable that radium inhibited a carcinoma present at the original treatment.

Inhibition of the cancer by the application of the x-ray as given also seems unlikely to have occurred since the dose reaching the uterus was only 400 r., obviously insufficient to affect an adenocarcinoma.

In a study of other ways in which these patients might be selected, there was nothing discovered in age, parity, economic status, or the nature of our local or hospital population. Conditions so widespread as abnormal bleeding at the menopause and fibromyoma determine a fairly unselected group.

Among the carcinomas of the cervix, there was one in an Orthodox Jewess. This was, however, an adenocarcinoma of the endocervix which may minimize the factor of immunity which women of this race seem to have against carcinoma of the cervix.

Fibromyoma was present in 54 per cent of the whole group and in 54 per cent of those who suffered from uterine bleeding, a proportion close to that obtaining in the general population and apparently without significance.

To the question as to whether the radiation employed might be a contributing cause of the carcinoma, we shall only refer to extensive evidence in the literature¹⁸ which indicates that radiation with techniques and dosages such as were employed in these cases is not a cause of carcinoma.

The only way in which these women differed widely from their fellows was that a very large proportion suffered from excessive uterine bleeding. As may be seen from Table VIII, this was present in 87.4 per cent of the cases; in 40 per cent the uterus was grossly normal and in 47.4 per cent myomatous. Bleeding was the symptom requiring treatment in all of the cases subsequently contracting carcinoma. This abnormal bleeding is decidedly out of line with the experience of women in general who are approaching the menopause, among whom only 13 per cent suffer from excessive bleeding, while the other 87 per cent either stop abruptly or taper off gradually.¹⁹ There appears then in this group to be a definite correlation between bleeding prior to the menopause and the

subsequent appearance of carcinoma. This implies that there is some anatomic or physiologic factor which makes these uteri fertile ground for the subsequent neoplastic process.

TABLE VIII. INDICATIONS FOR RADIOTHERAPEUTIC MENOPAUSE IN 722 OF THE 958 REPORTED PATIENTS

INDICATION	NO. OF PATIENTS	PER CENT
Total Bleeding	631	87.4
<i>Without fibromyoma</i>		
Menstrual excess	117	16.2
Intermenstrual bleeding	172	23.8
<i>With fibromyoma</i>		
Menstrual excess	171	23.7
Intermenstrual bleeding	171	23.7
Fibromyoma without bleeding	58	8.0
Other*	33	4.6
TOTAL	722	100.0

*Cases of artificial menopause for dysmenorrhea, endometriosis, sterilization, and non-pelvic conditions (headache, epilepsy, tuberculosis, etc.)

TABLE IX. DISTRIBUTION BETWEEN CORPUS AND CERVIX OF CARCINOMA OF THE UTERUS SUBSEQUENT TO RADIATION FOR BENIGN CONDITIONS

SOURCE	CORPUS	CERVIX
Scheffey		
Collected	40	18
Personal	12	7
Burnam	5	3
Sloane Hospital		
This study	9	6
First treated elsewhere	5	1
Total	71	35

This impression is strengthened by the unusually high proportion of carcinomas of the corpus of which there were nine as against 6 of the cervix, a proportion which is in agreement with that reported by other authors. In Table IX we have combined the cases collected and those personally reported by Scheffey,⁹ those of Burnam,²⁰ and those of this study, together with 6 further cases observed by us but having had their radiotherapeutic menopause elsewhere. There are 106 cases of carcinoma of the uterus, of which 71 were in the corpus and 35 in the cervix, a ratio of 2 of the corpus to 1 of the cervix, a ratio six times as great as that existing in our clinic, which is 1 of corpus to 3 of cervix and fourteen times as great as the rate usually accepted (1 corpus to 7 cervix).^{21, 22} Objection may be made that the normal ratio should be that for carcinomas occurring at the same ages at which they occurred in our series, where the average age was 55.1 for the cervix cases and 56.2 for those of the corpus. The ratio of corpus to cervix in our clinic at these ages is as 1 to 2, making the ratio in the 106 cases here reported four times as great. By whatever calculation, there is a significant increase in the proportion of corpus carcinoma.

Another interesting finding is an apparently high incidence of endometrial hyperplasia in the uteri which subsequently contracted carcinoma. Five of the 6 specimens examined showed, at the original curettage, cystic and glandular hyperplasia, while this was found in only one-third of the specimens taken

from the whole group of 958 patients. This observation agrees with that of Taylor²³ and is worthy of further study.

Still another unusual finding is the high incidence of endocervical carcinoma, 4 being in this region and only 2 on the portio. Of the 4 endocervical carcinomas, 2 are adenocarcinomas.

We conclude, then, that the high incidence of cancer of the uterus is largely due to the excess of carcinoma of the endometrium, that these carcinomas have occurred in endometria which bled excessively before the menopause and showed a higher incidence of hyperplasia. The nature of the processes or stimuli which brought about this combination of circumstances is food for interesting speculation and further study, but is beyond the scope of this paper.

The clinical application of these observations will depend on how seriously these figures are taken. Assuming that more extended studies will confirm our estimate that 9.6 per cent of women 30 to 55 years of age, requiring treatment for excessive uterine bleeding, etc., will sooner or later contract carcinoma of the uterus, we must decide whether this threat is sufficient to warrant a prophylactic complete hysterectomy, a procedure necessary to afford complete protection from subsequent carcinoma. In the cases in which hysterectomy is required because of the large size or of changes in a myoma, pedunculated submucous fibromyoma, coincident adnexal disease, undesirability of the menopause, etc., one need only to decide whether to perform a partial or complete hysterectomy. In the cases which would be proper subjects for an artificial menopause, the choice will lie between a simple procedure and a major operation. Following a sterilizing dose of radiation, bleeding will be controlled in 98 per cent of the cases and the myomatous mass will shrink satisfactorily in 95 per cent.²⁴ The procedure entails no mortality and little disability. The mortality from complete hysterectomy varies greatly in different clinics and is usually in inverse proportion to the number of operations performed, varying from 0.7 per cent²⁵ up to 6 per cent. When performed on uteri which would be proper subjects for an artificial menopause, it should present little technical difficulty and should be accompanied by the least danger. Nevertheless, in the past, dangers of prophylactic hysterectomy would have made such a routine practice unwise. In the future, improvements in the management of shock, hemorrhage, infection and thrombosis, and an elevation of the general level of surgical efficiency, should so lower the dangers of complete hysterectomy that it would be small compared with the threat of subsequent carcinoma. With this prospect, on the one hand, of lowering the operative risk and, on the other, of an increase in the already large number of carcinomas due to a still further increase in the proportion of people at the older ages, the element of prophylaxis should receive serious consideration in planning the treatment of a woman suffering from abnormal uterine bleeding.

Conclusions

1. Among 958 patients treated for benign uterine bleeding by the radiotherapeutic menopause and followed for 6.7 years each, on the average, there subsequently occurred 15 carcinomas of the uterus. Based on modified mor-

tality statistics, the same number of women in the general population during the same length of time should contract 4.4 carcinomas of the uterus. The observed number of cases is therefore 3.4 times as large as the number expected.

2. Two and eight-tenths per cent of women in the general population between the ages of 30 and 55 years contract cancer of the uterus before reaching the age of 80. Applying the above ratio of 3.4 we find that 9.6 per cent of women suffering from uterine bleeding prior to the menopause would contract the disease.

3. Of 15 cases, 9 were of the corpus and 6 of the cervix. This abnormal preponderance of carcinoma of the corpus is in agreement with that present in other reported cases in which the ratio is two of corpus to one of cervix. This ratio of corpus to cervix is six times that obtaining in our clinic.

4. It is inferred that the endometria of uteri which bleed abnormally prior to the menopause are predisposed to the subsequent development of carcinoma of the corpus.

5. Prophylaxis against carcinoma of the uterus should be an important factor in a plan of treatment for uterine bleeding prior to the menopause.

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THE VALUE OF PHYSIOLOGIC SUBSTRATES IN SPERM MIGRATION IN SELECTED CASES OF HUMAN INFERTILITY

Observations on a Series of 106 Patients

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THE reproductive process of man is indeed complicated in comparison with other species. As the processes of living become more specialized, survival of the species depends not so much upon being the "fittest," as upon the proper and efficient coordination of the intricate mechanism of reproduction and its complex psychological and economic elements.

In the mosaic of the intricate physiologic patterns and processes so essential to this biologic symmetry in fruitful reproduction, one can evaluate many of those factors requisite to the attainment of such an orderly physiologic progression in the reproductive organs of each sex. Much attention is paid to the major facets. The medical literature is replete with considerations of patency and nonpatency of the oviducts, congenital malformations, anovulation, so-called hostile cervical secretions, endocrinal imbalances, and other aspects which contribute to human infertility and sterility. There has been little stress laid upon the importance of other physiological variants which play vital roles in the complex process of human reproduction. Other problems to be considered with serious attention include the mechanisms of copulation, the biochemistry of the lower genital secretions in each sex, biochemistry of the ejaculate as related to the metabolism of its living cells, and the progressive continuity of fluid pathways for sperm migration. The alterations in vaginal flora also should receive consideration in all patients being studied for infertility.

The author wishes to present in this paper his experience with two of these problems, a consideration of the fluid pathways in the female for sperm migration and their influence upon sperm motility. In certain cases, selective in the sense that the major organic obstacles to fruitful impregnation are absent, it is possible that these minor physiologic and biochemical imbalances assume a major responsibility for continued infertility unless they are corrected. In a series of 106 barren couples studied, with these probabilities in mind, it was possible to obtain 29 successful impregnations wherein the treatment introduced was only the addition of a precoital physiologic substrate to insure a proper fluid pathway continuity which would meet the metabolic requirements of spermatozoa during their migration.

Animal Husbandry Experience With Physiologic Substrates and Spermatozoa

Prior to a discussion of this series, it was thought advisable to review some of the valuable data on animal infertility. Marshall,¹ thirty-five years ago,

observed the chemical differences which exist between the spermatozoa of the different species and orders did not show any connection with the zoological relationship.

Baker,² 1930, was among the first to use a buffered glucose saline fluid for keeping mammalian sperm in an active state at body temperature. Ivanov,³ 1931, was the first to point out that motility in dog spermatozoa was little correlated to states of anaerobiosis except that greater concentrations of sperm under anaerobic conditions displayed an earlier loss of motility. Today this can be explained by a greater number of spermatozoa utilizing the available glucose in the process of anaerobic glycolysis. Hyme,⁴ 1932, prolonged the motility of guinea pig sperm in an isotonic Ringer-glucose substratum.

Redenz,⁵ 1933, related the modern view on cleavage metabolism of glucose to mammalian spermatozoa in relation to their motility. Bernshtein⁶ observed that while nutrient substances in the substrate increase the motility, his solutions did not cause an increase in the survival time of the sperm. In a later paper, however, Bernshtein⁷ did note that while the semen is outside the body, the glucose concentration of the fluid falls, but that of the spermatozoa remains relatively constant. Bernshtein and Slovachotov⁸ reported, 1933, that fresh ejaculates of the bull *and man* contain about 40 mg. per cent of lactic acid which increases in the semen kept outside the body. They found the motility of the spermatozoa gradually decreases, but *its complete cessation occurs at different lactic acid levels.*

Ivanov⁹ found, 1936, that the respiratory quotient of sheep spermatozoa approached unity in the presence of glucose and departed from unity in the absence of sugar. He¹⁰ reported, in the same year, that the respiratory quotient of sheep spermatozoa in Ringer's solution alone was considerably less than unity and that the oxidation of lactic acid did not play any significant role in the respiration of spermatozoa in saline media.

Lloyd¹¹ and Anderson¹² independently pointed out the additional value of buffering animal sperm dilutors. The former found a pH of 7.5 isotonic glucose-saline dilutor to give more satisfactory, clinical results, while Anderson obtained his optimum results with the glucose-saline isotonic substrate at a pH of 7.6. It seems significant that each author arrived at practically the same pH and considered the importance of isotonic solutions.

Warbuton, McKenzic, Berliner, and Andrews,¹³ at the Thirtieth Annual Meeting of the American Society of Animal Production, 1937, were among the first to consider the relationship of pH along the entire course of the genital canal to sperm motility. They made pH determinations on the contents of the tubes, uterine horns, cervix, and vagina of inseminated ewes. They showed pH differences of as much as 0.8 unit for the two tubes and 0.4 unit for the two uterine horns of the same animal. The cervix was usually the most acid region, pH 6.1 to 7.6, and sperm remained normal there longer than in the rest of the genital tract. It was observed that the acidity developed in relation to the disappearance of the sperm. It must be recalled, however, that the ram has a more adaptable copulative mechanism to insure the deposit of sperm into the favorable cervical environment.

Phillips,¹⁴ 1939, reported a case of bovine impregnation from bull semen after preservation in an egg yolk buffer solution at a pH of 6.7 for as long as 100 hours. His evidence includes documented records of pregnancy. Milovanov,¹⁵ 1938, described an unique and very successful way to artificially inseminate farm animals with gelatinized sperm. Considerable care is taken with the insertion of these capsules into the more favorable cervical and uterine substrate.

Webster,¹⁶ 1939, in his investigations on sheep semen found the seminal plasma had a high content of glucose, while the acid drift was associated with degradation of the glucose to lactic acid. It is not improbable that variable quantities of seminal glucose in different animal semen bears a reasonable correlation to the survival times. Telesforo¹⁷ observed that there existed variable time limits for storage of semen: for cattle, semen from 50 to 120 hours; sheep, 75 to 120 hours; horse, 12 to 24 hours; and for the pig, 1 to 2 hours.

Davis and Williams,¹⁸ 1939, studied variations in pH of the bull semen following repeated ejaculations. They observed that the average pH of the first ejaculate was 6.85; the

second, 7.23; and a third ejaculate, 7.21. They noted a significant correlation between the concentration of spermatozoa per cubic millimeter and the pH; the higher the concentration the lower was the pH. Comstock,¹⁹ 1939, observed that glycolysis decreased as sperm aged. Smith and Asdell,²⁰ 1940, reported that the buffering capacity of semen decreases with age of the bull sperm. Stallion sperm loses its motility rapidly at any pH below 4.7 to 4.6.²¹ Stallion semen possesses much less glucose content than other animal semen.

Lardy and Phillips,²² 1941, point out that there is an active succinic acid dehydrogenase present in spermatozoa. Although glycolytic and oxidative processes probably furnish energy for motility under normal conditions, if both of these are blocked simultaneously, spermatozoa still can retain motility for considerable periods of time. Moore and Mayer,²³ 1941, observed an extremely variable sugar content in ram semen and conclude that the loss of mobility of the spermatozoa and sugar loss were often coincident.

Dougherty and Ewalt,²⁴ 1941, in a study of 645 semen samples from 104 bulls, observed little correlation between the laboratory findings and breeding efficiency of the bulls, save for those conclusions which demonstrated a positive correlation between pH changes of semen in the first few hours and the motility and viability of spermatozoa. Swanson and Herman²⁵ determined that the factor most indicative of a bull's fertility was the length of time vigorous motility was maintained. Knoop,²⁶ 1941, was able to maintain cell life in bull sperm for 16 to 35 days using one buffered gelatin-egg yolk diluent, and 14 to 38 days with an egg yolk-buffered salt diluent.

Henle and Zittle,²⁷ 1942, demonstrated that differences in the maturity of bull spermatozoa played a role in oxygen consumption, seminal spermatozoa showing a lower rate than epididymal cells.

Lardy and Phillips,²⁸ 1943, report significant metabolic changes in bull, cock, and rabbit spermatozoa after varying certain electrolytes in their substrates. Varying the phosphate ions affected the glycolysis and motility of sperm in the presence of glucose. These processes were greatly depressed in the absence of the phosphate. The omission of magnesium ions from the medium depressed cellular respiration. Manganese and calcium ions affected motility, glycolysis, and respiration adversely. At least 0.005 mg. of potassium was necessary for the maintenance of optimum motility, while this and even higher concentrations stimulated respiration and glycolysis. We see in this excellent observation the tremendous importance of a balanced physiologic substrate to sperm metabolism. In a later paper these authors,²⁹ 1944, in discussing metabolism of bull spermatozoa concluded that phospholipids were evidently the source of intracellular reserve energy of spermatozoa. This energy is obtained by oxidative processes, and sperm *preferentially* obtain the energy for motility from the glycolysis of glucose or other glycolyzable sugar.

Green,³⁰ 1940, in a study on the chemistry and cytology of the sperm membrane of sheep characterized it as an albuminoid with the material remaining after extraction high in nitrogen content. Trypsin did not attack it and only slight action was noted with pepsin. This author suggests the use of acetocarmine stain and dark-field illumination in the evaluation of sperm quality in this species.

Day,³¹ 1940, considers that stallion sperm fertilizability appears to depend on the total number of active sperm while the small number of abnormal sperm had no bearing on fertility.

Frank, Smith, and Eichom,³² 1941, using a bull sperm diluent of embryonic tissue extract (10- to 13-day-old chick embryos) were able to prolong the life of the sperm remarkably. They report sperm viability for 22 to 46 days and observe that the fertilizing power of semen was not apparently altered.

Min-Chuch Chang,³³ 1942, implanted stilbestrol tablets in rams and followed this procedure with daily injections of 15 mg. of stilbestrol dipropionate for 31 days. Sperm production increased 7 to 9 days after the implantation, in proportion to the dosage. The effect lasted five days. Fertility was proved by artificial insemination tests. There was no effect on sex drive, sperm morphology, or quality of spermatozoa, although a strong tendency to sperm agglutination was noted after treatment.

It is unfortunate the excellent work of Hammond,³⁴ in 1927, upon the vaginal discharges of the cow have not been brought up to date. Up to this period, however, those histologic and cytologic observations summarize much more fundamental data on the lower generative tract than is available in any other modern single source. He considers the physical properties of mucus from the vagina to the uterus in great detail. Some day this wider approach may be considered in human fertility.

The animal husbandry aspects emphasize the value of physiologic substrate³ to sperm motility, sperm migration, and correlative biochemical factors present in the substrate along the genital canals of each sex. The investigators in the animal husbandry field of infertility have demonstrated rather conclusively the equal importance of considering the biochemistry of these genital secretions to sperm as biologic tissue, as compared to the clinical specialists in gynecology who overestimate the primary organic obstacles to the neglect of these basic biochemical and cytologic factors.

Experience With Physiological Substrates and Human Sperm

The modern study of human spermatozoal metabolism is relatively recent. The application of fundamental observations from studies on animal spermatozoa to the field of human fertility or infertility was tremendously sporadic in nature until the last half decade. The medical literature, aside from intermittent and unapplied biochemical observations arrived at largely through the curiosity of a few lone workers, was almost as barren of therapeutic considerations of these factors as could be possible.

MacLeod,³⁵ 1939, repeating earlier investigators¹⁻⁵ animal studies on sperm, using human specimens, came to the same conclusions, that human spermatozoal metabolism was almost exclusively a process of anaerobic glycolysis. He observed that maximum motility of human sperm suspended in Ringer-glucose solution was maintained for over three hours under anaerobic conditions, but decreased markedly in the same period in the presence of air or pure oxygen. In a later paper MacLeod³⁶ noted that, while the sperm glycolysis remained relatively constant from specimen to specimen, *large differences were found from individual to individual*. When the respiration of human spermatozoa was studied³⁷ in Ringer-phosphate media without glucose it was of such small magnitude that its existence was doubtful.

Zagami,³⁷ 1939, reported at length upon the chemical composition and physiochemical properties of seminal fluid. He discusses the density, pH, relative viscosity, surface tension, and other properties in his comparisons of the seminal fluid of man, dog, rabbit, and the cock.

Shettles,³⁸ 1940, observed that the rate of respiration of human spermatozoa varies inversely with the age of the specimen and directly with the number of cells per unit volume. Shettles was the first to record that human spermatozoa remained most active for several hours in pure nitrogen, nitrous oxide, helium, and in air reduced to a very low pressure. He observed that carbon dioxide in excess produces complete immobility within a few minutes and the motility can be restored when this gas is replaced by nitrogen, air, or oxygen. He was able to revive some human sperm from very low temperatures and have them remain active for several hours.

Zeller and Joel,³⁹ 1941, demonstrated that in human sperm cholinesterase and diamine oxidase occurred only in the plasma and not in the spermatozoa. The latter is derived principally from the seminal vesicles. These writers showed that compounds which react with the carbonyl group can decrease the motility of spermatozoa in low concentrations and increase motility in higher concentrations.

MacLeod,⁴⁰ 1943, using human cells, arrived at the same conclusions that Lardy and Phillips²² reported on the bull spermatozoa. He found that succinic acid was oxidized but this reaction was not coupled with motility.

Ross, Miller, and Kurzrok,⁴¹ 1941, found that sperm from men who were definitely fertile, probably fertile, and suspected of impaired fertility, all utilized glucose aerobically

in Ringer-carbonate media, in human follicular fluid and in semen. It is noteworthy to mention that, while these authors state they could determine no significant quantitative changes among the three groups of men, they did report that lesser quantities of oxygen were consumed by three specimens from men probably infertile.

MacLeod,⁴² 1941, in a study on the effect of certain substrates upon the metabolism and motility of human spermatozoa noted that deprivation of sugar at 38° C. caused failure of motility within two to four hours. These sperm could be revived again upon the addition of glucose if the spermatozoa had not been exposed to oxygen during the period of deprivation or if they had not been inert longer than thirty minutes. In this paper MacLeod discussed the possible application of these time relationships to the behavior of human spermatozoa in the male and female genital tracts. MacLeod and Hotchkiss⁴³ observed that 75 per cent of the human spermatozoa are found in the first 40 per cent of the normal ejaculate while the last portion of the split-ejaculate contained a higher concentration of glucose.

Hoagland and Pincus,⁴⁴ 1942, were able to report the revival of human and animal sperm after immersion in liquid nitrogen if they were later rapidly warmed to 35° C. by plunging them into a suitable and balanced isotonic medium.

The Clinical Use of a Precoital Physiologic Substrate in Human Infertility

Recently, MacLeod and Hotchkiss,⁴⁵ aware of the possible role of the isotonic media to the metabolism and motility of the human spermatozoa, utilized these biochemical principles in cervical applications in selected cases of human infertility. They reported 12 pregnancies in cases of long-standing infertility in which a precoital irrigation of the vagina with a balanced salt solution containing a high percentage of glucose was used. In the past three years 106 couples, exhibiting no obstructive pathology to sperm migration in the female partner and refractive to other routine antisterility therapy in one or both partners, were selected for clinical trial. In all instances, the sperm studies, endocervical studies, tubal insufflation or hysterosalpingography, and endometrial biopsies had been made.

The female partner was asked to record daily the basal body temperature readings. She was advised to add the carefully weighed solid salts of a Ringer-glucose mixture* to an exact amount of tap water. During her relatively fertile period, as determined from her individual basal body temperature chart, the patient preceded intercourse with a vaginal irrigation, using this balanced isotonic substrate as the solution. Care was taken to insure a retention of several cubic centimeters of this solution in the vaginal canal and intercourse followed soon after. In two successful cases the Ringer-glucose solution was used prior to artificial insemination. In 27 other cases the women were found pregnant between one and seven months after such simple treatment. Twelve cases, 40 per cent, conceived within the first fertile period in which the artificial substrate was added as a precoital irrigation. *In 19 cases the Huhner test was found positive after use of a precoital sugar douche wherein previous Huhner tests, without the use of the glucose substrate, were found negative.*

A survey of Table I will reveal the summarized individual observations of the 29 cases to successfully conceive following the use of a precoital Ringer-glucose irrigation. The period of infertility had varied between one and twelve years. The age of the patients ranged between 23 and 44 years.

*The Ringer-glucose salts used to prepare the isotonic substrates can be obtained under the commercial name of Nutri-Sal from Ortho Products, Inc., Linden, New Jersey.

TABLE I

CASE	AGE (YEARS)	LENGTH OF MAR- RIAGE (YEARS)	LENGTH OF STE- RILITY (YEARS)	FACTOR OF STERILITY	HUHNER TEST BEFORE AFTER RINGER-GLUCOSE		KURZROK- MILLER TEST	CONCEPTION FOLLOWING USE OF RINGER- GLUCOSE (MONTHS)
767	44	4½	4½	Negative Huhner	0	+	+	5
924	34	7½	6½	Oligospermia	0	Not done		1
970	30	3	1	Negative Huhner; cervicitis	0	Not done		1
624	30	4	1	Conical cervix; oligospermia	0	+	+	5
761	26	5	2½	Cervicitis; nega- tive Huhner	0	Not done		1
772	36	14	3	Cervicitis	0	+		3 (aborted at 10 weeks)
C.M.	24	3	1½	Oligospermia	0	+		3
520	31	12	12	After 9 monthly attempts of arti- ficial insemina- tion with no suc- cess advised use of Ringer-glucose prior to insem- ination	Not done	Not done		1
280	28	6	6	Oligospermia	0	+		2
326	29	5	5	Oligospermia	0	Not done		2
770	39	1½	1½	Oligospermia	0	+	+	3
698	32	1½	1½	Oligospermia	0	Not done		1
871	23	3½	2¾	Negative Huhner	0	+		2
273	35	8	1	Negative Huhner; oligospermia	0	+		2nd pregnancy following vaso- epididymal anastomosis
817	34	8	6	Oligospermia	0	+		4
771	35	10	1½	Cervicitis	0	+	Nega- tive	5
850	38	5	5	Oligospermia	0	+	Nega- tive	7 (aborted at 2 months)
575	30	9	9	Negative Huhner	0	+		2
815	25	4½	2	Negative Huhner with trichomonas	0	+		3
E.P.	27	2	2	Cervicitis; oligo- spermia	Not done	Not done		1
378	29	3	2	Negative Huhner	0	Not done	+	1
424	33	9	4	Negative Huhner	0	Not done	+	2
504	31	8 (1 previous pregnancy 8 years)	8	After 5 monthly attempts of arti- ficial insemina- tion with no suc- cess, was advised to use Ringer- glucose prior to insemination	Not done	Not done		1
873	26	2½	1½	Oligospermia	0	+	Nega- tive	1
845	29	4	3	Oligospermia; thick cervical plug	0	+	+	1
876	27	5	5	Oligospermia	0	+	+	4
852	32	8½	2	Negative Huhner	0	+	+	1
724	28	6	3	Cervicitis	0	+	Nega- tive	1; ectopic preg- nancy
894	32	7	5	Cervicitis	0	+	Nega- tive	2

There were 76 other cases having cervicitis and/or oligospermia with negative Huhner tests in which a Ringer-glucose douche was advised and used, with no success.

All of the Huhner tests were done at or near ovulation time. Repeat examinations were usually made either in 48 hours, or the following month.

Most cases used Ringer-glucose solution during the "fertile period," as recorded by basal body temperatures.

Many of the successful cases had other examinations, performed prior to the use of Ringer-glucose solution, such as the study of endocervical secretions, tubal insufflation, hysterosalpingography, and endometrial biopsy.

There occurred four fetal losses, by spontaneous abortion in three cases and ectopic pregnancy in one case, giving a fetal loss of 13.4 per cent or about equal to the average fetal loss encountered in conceptions following normal copulation.

The important consideration is that among 106 barren couples 29 women (28.3 per cent) were able to conceive following no other therapy than the simple use of a precoital Ringer-glucose irrigation used at the individual "fertile period" as determined by the use of basal body temperature graphic records. In all instances, previous and more time-consuming and expensive infertility therapy of both or one partner had failed. One cannot escape the conclusion that this success was realized largely because of our attempt to capitalize upon known biochemical observations already extant in animal husbandry and the preclinical medical writings. The success again illustrates the rewards of simplicity in therapy when once the basic truths are available for *in vivo* application.

Discussion

When one reflects seriously about the purposes behind copulation other than the recognized need to attract the opposite sex to the other partner, there seem to exist other specific physiologic functions in the copulative mechanisms. During coition there is an admixture of vestibular gland secretions, cellular debris, cervical mucus, vaginal exudate, smegma from both individuals, Cowper gland secretions, reflux urinary droplets, bacterial flora from each partner's lower genital tract, in addition to the ultimate male ejaculate arriving at the orgasm. Is it amiss to compare the intrust and outthrust of the male phallus in the copulative act to a biologic pestle thoroughly mixing the surface secretions in the receptive vaginal mortar to insure a uniformity of a physiologic substrate from these biochemical components possessing variable physical properties? The timing of the male orgasm to occur at the termination of this biologic act would seem to represent the most favorable moment when the surface secretions, so essential to maintenance of metabolism and sperm migration, were most favorably mixed to assure favorable deposition of the male cells. The female orgasm frequently induces early sleep, thus obviating increased chances of disturbing these biochemical relationships and conditions prepared during copulation for the most favorable sperm reception.

The vaginal precoital pH range is 3.4 to 5.0, while in the postcoital examination we find a pH range of 4.4 to 6.2 in the normal canal and a postcoital range of 6.0 to 7.4 in women exhibiting amenorrhea in prepubertal and menopausal ages.⁴⁷ The pH of the cervix ranges between 8.0 and 9.0 both precoitally and postcoitally. *The significant changes in pH occur in the vaginal canal and the seminal pool.* These findings seem to corroborate our previous considerations anent the function of copulative mechanics; i.e., there is a definite purpose in the phallic mixing of male and female secretions to insure receptive surface substrates. Because of these findings the writer cannot agree with Greenhill⁴⁷ that the pH plays little or no part in sperm metabolism although it must be considered but one facet of the biochemistry in the fluid pathway for sperm seeking cervical and uterotubal ingress.

It does not appear improbable that the use of a Ringer-glucose precoital irrigation, at the most favorable period, accomplishes several real contributions toward increasing the possibilities for sperm migration by furnishing additional sugar and isotonic electrolytes for stimulation of cellular metabolism and motility, through promotion of a propitious pH of the mixture of the vaginal secretions, by altering the viscosity of both the distal cervical mucus and the male ejaculate in the presence of a favorable isotonic substrate, and by providing a less abrupt metabolic shock for the spermatozoa.

When one considers the manifold aspects which can alter the surface substrates and glucose levels of the semen in the vaginal secretions, it becomes more obvious that Ringer-glucose isotonic solution used as a precoital irrigation does merit a definite place in the armamentarium of the physician confronted with infertility problems.

Summary

Evidence is cited to indicate the importance of physiologic isotonic substrates to sperm metabolism and motility.

The application of these important animal husbandry and preclinical laboratory observations to the relief of human infertility, in carefully selected cases, is discussed. Among 106 such couples, giving a history of 1 to 14 barren years, Ringer-glucose isotonic solution was used precoitally as a vaginal irrigation, and the author is able to report 29 successful conceptions, a salvage of 28.3 per cent from this group of infertile patients.

This procedure, because of its simplicity in application, is worthy of extended clinical trial and is recommended in those cases of infertility exhibiting no obstructive organic pathology.

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POSTMENOPAUSAL ENDOMETRIUM AND ITS RELATION TO ADENOCARCINOMA OF THE CORPUS UTERI

A Study of 236 Cases*

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THE question of whether a given malignant neoplasm passes through a premalignant phase often is raised and hence should be considered as fundamental. Since the problem obviously is closely allied with early diagnosis and treatment, the question is not purely academic but practical as well. Thus, if a premalignant phase definitely could be established, physicians could strive to diagnose the condition during this period and eradicate it, with consequent prevention of the malignant neoplasm. The foregoing fundamental question prompted a study of the postmenopausal endometrium and its relation to adenocarcinoma of the corpus uteri.

In the many previous studies that have been reported in the literature, diversity of opinion has arisen because of lack of preciseness in the use of terms such as "hyperplasia" and "hypertrophy" and because of attempts to give these histologic terms a clinical significance. The definition of the term "hypertrophy," according to Boyd,^{1,2} is an increase in the size of individual cells or fibers as a result of which the organ may become enlarged. Enlargement of an organ from any other cause should not be called hypertrophy. The term "hyperplasia" means an increase in the number of cells of a part. Its limits are less well defined than those of hypertrophy and it might gradually merge into the process of neoplasia.

The term "endometrial hypertrophy" was introduced by Cullen³ in 1900 and later was adopted by Novak and others. In 1915, Novak⁴ recognized the difference between so-called hypertrophy and what he thought to be another entity, namely, hyperplasia, and thus he introduced into the literature the term "endometrial hyperplasia." This term immediately acquired a clinical connotation which largely supplanted any precise histologic definition which it originally might have had. The microscopic picture usually denoted as endometrial hyperplasia is one of great glandular proliferation with complete absence of luteinic change and decidual reaction. The glands may be lined by several layers of cells and there may be some degree of invasion of the muscular wall. The deeper glands may show cystic dilatation, giving what Novak called the "Swiss-cheese

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appearance." The stroma is abundant, and the superficial layers may show patchy necrosis, hemorrhage, and infiltration with inflammatory cells. Follicular cysts of considerable size may be present in one ovary; the other ovary may be shrunken and sclerotic. There is a notable absence of corpus luteum.

Herrell and Broders⁵ expressed the opinion that such terms as "endometrial hypertrophy" and "endometrial hyperplasia" convey little information with respect to the histologic appearance of the endometrium. They maintained that the differentiative phases in the menstrual cycle repeatedly have been confused with hypertrophy. These investigators also stated that they preferred the term "cystic endometrium" to the term "Swiss-cheese hyperplasia" or "cystic hyperplasia." They pointed out that cystic endometrium has been diagnosed by some as hypertrophied endometrium and expressed the opinion that this cystic condition accompanies clinical ovarian failure or the approaching menopause rather than hyperplasia. Furthermore, they said that sudden withdrawal or failure of ovarian tissue is accompanied by true atrophy which consists of loose stroma with a few nonfunctioning basal and subbasal glands.

The presence of subbasal glands, as described by Herrell and Broders, has been said by various investigators to be pathognomonic of the menopausal age and even pathognomonic of hyperplasia. These workers have claimed that this process is identical with external adenomyosis. Herrell and Broders, however, observed the presence of these structures during all phases of the menstrual cycle, and also at all ages from intrauterine life (endometrium of a fetus, 30 weeks of age) to twenty years past the menopause.

In this paper such terms as "endometrial hypertrophy," "endometrial hyperplasia," "cystic hyperplasia," and "Swiss-cheese hyperplasia" will not be used except as necessary in review of the literature.

Review of Literature

The histology of the normally and abnormally functioning adult endometrium has been thoroughly studied in recent years. The alterations which occur during the normal menstrual cycle and the changes produced by different types and degrees of ovarian failure have been described by many writers. The postmenopausal endometrium has received little attention, however, and it usually is assumed that after the menopause the endometrium merely becomes atrophic. Most textbooks of pathology, for example, allude to the postmenopausal endometrium as being atrophic. Undoubtedly every pathologist has seen endometrium removed years after the menopause which histologically resembled that removed during the period of active menstrual function. A careful search of the literature, however, revealed only a few reported studies concerning the frequency of occurrence of this type of endometrium.

In 1941, Novak and Richardson⁶ reported that the traditional concept of the senile endometrium as extremely atrophic was borne out in only 62 of 137 cases. Thirty-eight (27.7 per cent) of the 137 cases which they studied had endometrium with proliferative activity comparable to that seen in the reproductive epoch.

There have been a number of studies of the endometrium in cases of postmenopausal bleeding. The most direct study of this kind was made in 1935 by Breipohl,⁷ who interpreted the endometrial changes as due to late ovarian activity.

The fact that endometrium corresponding to the proliferative variety in the menstruating female does occur after the menopause appears to fit in with the now well-established fact that estrogen may be found in the urine of females long after the menopause or after castration.

The majority of evidence points to the assumption that cystic and hyperplastic changes in the endometrium result from the excessive or unopposed action of estrin. This is most common during the latter part of the active reproductive period but may occur earlier. Novak and Martzloff,⁸ in 1924, noted that cystic and hyperplastic endometrium frequently is accompanied by ovarian follicular cysts. Nelson,⁹ in 1937, and others produced a comparable picture in the endometrium of experimental animals, and a cystic and hyperplastic endometrium is known to accompany the development of estrin-producing ovarian tumors.

The source of stimulus which produces activity in the postmenopausal endometrium is uncertain. Hofbauer,¹⁰ in 1931, found that anterior pituitary extract when injected into ovariectomized guinea pigs caused congestion of the uterus and slight but definite thickening of the basal layer of the uterine mucosa. The studies of Frank, Goldberger, and Salmon,¹¹ in 1936, on a group of women whose ovaries by the usual criteria were physiologically inactive, pointed to an extraovarian source of estrin. Novak and Yui¹² believed that the postmenopausal endometrial hyperplasia in their cases could be attributed to the production of estrin elsewhere than in the ovary. In considering the causes of late endometrial activity, Taylor and Millen,¹³ in 1938, mentioned several possibilities, namely, an ovarian hormone which comes from small functioning ovarian neoplasms, the late development of follicles or an extraovarian source.

The occurrence of follicular cysts, failure of ovulation, infrequent presence of corpus luteum, and hyperplasia of the endometrium in patients who have adenocarcinoma have been given as proof that hyperestrinism or the unopposed action of estrogen is the immediate cause of the malignancy.^{14, 15} Most authors agree that hyperplasia results from unopposed estrogenic effects. Hence, since some observers believe that hyperplasia is precarcinomatous, it is easy to see why the idea has arisen that excess estrogen leads to corporal carcinoma.

Gebhard,¹⁶ in 1892, maintained that malignant adenomas arise from hypertrophied glands in chronic endometritis.

In 1915, Schröder¹⁷ reported a case in which adenocarcinoma had developed in a uterus which was the seat of hyperplasia. In 1923, Meyer¹⁸ described two cases in which islands of adenocarcinoma were found embedded in the hyperplastic endometrium, much like implanted ova, and in one of these a direct transition from benign to cancerous regions was demonstrated. Horsley,¹⁹ in 1924, reported a case which "probably developed on an hypertrophic endometritis."

Taylor,²⁰ in 1932, reported 85 cases of hyperplasia, 50 cases of cervical polyps, and 152 cases of adenocarcinoma of the corpus uteri. He presented evidence, which was based primarily on the cases of adenocarcinoma, that hyperplasia may be a predisposing factor in the later development of carcinoma.

Taylor reported that carcinoma later was demonstrated in two of the 85 cases in which the original diagnosis was endometrial hyperplasia. Both of these instances of apparent transformation were found to be due to failure to detect the carcinoma on first examination. He said that these two cases "illustrate the practical dangers of a confusion of hyperplasia and carcinoma due to a failure of the malignant parts of the endometrium to reach the microscope or to an erroneous interpretation of morphology. They emphasized furthermore the criticism that must be applied to cases of apparent evolution of carcinoma from hyperplasia."

Finally, Taylor remarked that "whether from a practical standpoint hyperplasia is to be regarded as precancerous and treated as such must remain an open question. The relative frequency of hyperplasia undoubtedly indicates that the individual patient with the disease is reasonably safe. Nevertheless it appears that when hyperplasia is at all marked, the possibility of a predisposition to the development of cancer should be considered and the case regarded with the same degree of suspicion now bestowed upon the diffuse forms of hyperplasia of the breast epithelium."

Novak and Yui,¹² in 1936, reported the results of a review of all cases of endometrial hyperplasia and of adenocarcinoma of the body of the uterus which they had encountered during the previous eleven years. This entailed study of 12,813 specimens, among which they encountered 804 cases of endometrial hyperplasia and 104 cases of adenocarcinoma of the body of the uterus. Of the 804 cases of endometrial hyperplasia, 40 occurred in women more

than 55 years of age, an incidence of approximately 5 per cent. Of the 104 cases of adenocarcinoma of the body of the uterus, 61 occurred in women who were more than 55 years of age, an incidence of 58.6 per cent. Moreover, of the 61 patients, 13 (21.3 per cent) had associated hyperplasia of the endometrium. Of the 104 cases of adenocarcinoma of the body of the uterus, there were 64 in which both carcinomatous and noncarcinomatous mucosa was available for study. Of these 64 cases, 25 (39 per cent) had coexisting hyperplasia of the mucosa.

Since adenocarcinoma and hyperplasia were common, Novak and Yui felt that their simultaneous occurrence was a coincidence rather than an indication of any more fundamental relationship between the two. However, these investigators found it necessary to change this concept. They concluded, on the basis of the previously mentioned study of 804 cases of endometrial hyperplasia and 104 cases of corporal adenocarcinoma, that not only do adenocarcinoma and hyperplasia frequently coexist, but often, in the same case, and perhaps even in the same section, all grades of transition from frankly benign, to borderline, to obviously malignant histologic pictures are observed. Their observations seem to indicate that hyperplasia persisting after the menopause predisposes to the development of carcinoma. Since the only known cause of hyperplasia is persisting hyperestrinism, the natural assumption is that this factor of abnormally long-continued subjection of the endometrium to stimulation with estrin is the important predisposing influence.

TeLinde²¹ in discussing the paper of Novak and Yui pointed out that their findings differed from those of certain other investigators. He said, "It would seem that the most likely explanation is a difference in their interpretation of what constitutes the minimum histologic changes necessary to a diagnosis of hyperplasia." He furthermore said that there are no absolute criteria for diagnosis. TeLinde had studied the material of Novak and Yui and frankly admitted that their histologic interpretation of hyperplasia was more liberal than his. He also had studied the postmenopausal endometrium in twenty cases picked at random in his laboratory. In eleven cases (55 per cent) he found the same histologic picture which Novak and Yui had interpreted as hyperplasia. This 55 per cent incidence caused TeLinde to question the etiological significance of the 39 per cent in the carcinoma group reported by Novak and Yui. The following remarks by TeLinde are not only pertinent to the subject under discussion, but also applicable to certain other situations.

"If hyperplasia is a precancerous lesion one would expect a parallelism between the age incidence of hyperplasia and carcinoma. The greatest incidence of hyperplasia is in the fifth decade of life. After fifty the incidence of hyperplasia decreases but the incidence of adenocarcinoma increases, so instead of a parallelism in their incidence there is a divergence. I have assured innumerable women in the late forties or early fifties who have had recurring bleeding due to hyperplasia that after getting past the menopause their chance of further trouble due to the hyperplasia would be nil. I have never had one of these women return with carcinoma of the endometrium. But even if an occasional one is later a victim of carcinoma, is it more than one might expect on the law of chance?

"If we are to change our concept of hyperplasia from a purely benign lesion to a precancerous one, the next logical step is to modify our present conservative treatment in a radical direction. This I feel would be a mistake, and it is with the thought of preventing unnecessary radical surgery or radiation that I have brought up these objections to the acceptance of an attractive theory which does not coincide with my clinical or pathologic experience."

Heurlin,²² in 1911, in a study of 44 cases of primary adenocarcinoma of the body of the uterus did not find evidence of associated hypertrophy of the endometrium but on the contrary he found an atrophic condition.

Payne,²³ in 1937, studied 2,070 sections from 534 cases (496 premenopausal and 38 postmenopausal) of endometrial hyperplasia. In the latter the time elapsing since the menopause was one to twenty-three years. In 13 of the 534 cases (2.4 per cent) there was associated carcinoma of the corpus uteri. He pointed out that if hyperplasia predisposes to carcinoma, the incidence of malignancy should exceed 2.4 per cent. Carcinoma occurred five times more often in the postmenopausal cases than in the premenopausal cases, yet

TABLE I. COMPARISON OF ENDOMETRIUM IN ADENOCARCINOMATOUS AND NONADENOCARCINOMATOUS CORPUS UTERI

DESCRIPTION AND NUMBER OF CASES	EARLY PROLIFERATIVE ENDOMETRIUM			LATE PROLIFERATIVE ENDOMETRIUM			ATROPHIC ENDOMETRIUM			EARLY PROLIFERATIVE AND ATROPHIC ENDOMETRIUM			LATE PROLIFERATIVE AND ATROPHIC ENDOMETRIUM		
	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†	CASES	PER CENT*	TOTAL†
<i>1. Classification of Nonadenocarcinomatous Portion of Endometrium in Eighty-Six Cases of Adenocarcinoma</i>															
Adenocarcinoma, grade 1 (21 cases)	8	38.1	11	5	23.8	8	2	9.5	8	3	14.3	3	3	14.3	14.3
grade 2 (23 cases)	11	47.8	14	2	8.7	4	5	21.7	10	3	13.0	2	2	13.0	8.7
grade 3 (15 cases)	3	20.0	6	6	40.0	7	2	13.4	6	3	20.0	1	3	20.0	6.7
grade 4 (27 cases)	6	22.2	10	9	33.3	13	4	14.8	12	4	15.8	4	4	15.8	15.8
Total (86 cases)	28	32.6	41 (47.7%)	22	25.6	32 (37.2%)	13	15.1	36 (41.8%)	13	15.1	10	10	15.1	11.6
<i>2. Classification of Endometrium in 150 Cases Without Adenocarcinoma</i>															
Surgical (100 cases)	55		66	31		31	3		14	11					
Necropsy (150 cases)	14		19	26		28	3		10	5		2			
Total (150 cases)	69	46.0	85 (56.7%)	57	38.0	59 (39.3%)	6	4.0	24 (16%)	16	10.0	2	2	10.0	1.3

*Percentages opposite grades 1, 2, 3 and 4 represent per cent of cases for respective grade of adenocarcinoma; percentages opposite total for adenocarcinomatous and nonadenocarcinomatous uteri represent per cent of 86 and 150 cases, respectively.

†Total cases that showed respective change, regardless of whether associated with other endometrial changes. Thus, some cases are counted in two groups.

postmenopausal corporal carcinoma generally is conceded to be three to four times as common as premenopausal regardless of the type of endometrium.

Jones and Brewer,²⁴ in 1941, studied 68 cases of carcinoma of the corpus uteri from the standpoint of histologic and anatomic evidence of ovarian and endometrial function. They pointed out that the various reports indicate that hyperplasia is not found with any great frequency in patients who have carcinoma. Therefore, they believed it logical to assume that estrogenic stimulation adequate to cause carcinoma also would stimulate the remaining portions of the endometrium to a greater extent than that which is found. These investigators also mentioned that experimental studies on the rat, mouse, guinea pig, rabbit, and monkey had demonstrated that administration of estrogens in large quantities over prolonged periods of time had produced cystic glandular hyperplasia of the endometrium but not carcinoma, and that carcinomatous changes were induced only when some carcinogenic agent was used simultaneously.

Jones and Brewer concluded that in the presence of endometrial carcinoma, the ovaries may function normally and the uninvolved portion of the endometrium may respond normally to ovarian stimulation. Thus, the etiological significance of hyperestrinism or the unopposed action of estrin in endometrial carcinoma was not demonstrable in their cases. The corpus luteum was normal even in those instances in which all the endometrium was involved in the malignant change. Taylor¹³ and Herrell¹⁴ likewise have reported that the corpus luteum occasionally is present and apparently functioning in patients who have endometrial carcinoma.

Shaw,²⁵ Cullen,³ and Burch and others²⁶⁻²⁸ have been inclined to deny that hyperplasia is a predisposing influence in the development of carcinoma. In the most recent paper by Burch,²⁸ he states, "I have never seen the two conditions associated in the same patient, nor have I ever seen hyperplasia as a forerunner to cancer."

Material and Method

Material.—The material studied consisted of gross and microscopic specimens of postmenopausal uteri, detailed descriptions of specimens and clinical and operative records of 236 cases of the Mayo Clinic. The 236 cases consisted of 86 cases in which the uterus had been removed because of adenocarcinoma, 100 cases in which the uterus had been removed for other reasons, and 50 cases in which routine necropsy had been performed.

In the majority of these cases careful examination of the uterus, tubes, and ovaries was possible, although in some cases only the uterus, and in others only the uterus and one ovary were available. In order to obtain suitable specimens for the study of uninvolved endometrium in carcinomatous uteri, careful selection was necessary. Uteri in which the carcinoma had involved more than half the endometrium were not used. The cases in which necropsy had been performed likewise were carefully selected in order to include only those in which the uterus was grossly normal and not involved by any pathologic lesion which might produce an abnormal condition.

Method.—Because of the paucity of information available concerning the postmenopausal endometrium and its relation to adenocarcinoma of the corpus uteri, it was decided to study the problem from three standpoints: namely, (1) classification of uninvolved endometrium in cases of adenocarcinoma of the corpus uteri, (2) classification of endometrium in cases without adenocarcinoma of the corpus uteri, and (3) a comparison of endometrium in adenocarcinomatous and nonadenocarcinomatous uteri.

From two to six blocks were made through the wall of the uterus so that the full thickness of the endometrium, together with a sizable portion of myometrium, was included in each section. Each block was taken from a different portion of the interior of the uterus so that all the endometrium out toward the horns, as well as down to the endocervix, was included in so far as possible. At least one section was taken through the adenocarcinomatous region in those uteri in which a malignant lesion was present.

On microscopic examination the lesions were graded from 1 to 4 after the method of Broders.



Fig. 1.—Atrophic endometrium. Section reveals single layer of surface epithelium with one gland present in the field ($\times 70$).

The endometrium was classified according to the method used by Herrell and Broders⁵ in their study of the endometrium of women during the period of the normal menstrual cycle. Although the endometrium was classified as "early proliferative," "late proliferative," and so forth, and from the histologic standpoint may have been indistinguishable from that of the normally menstruating female, we are aware that the tissue may not have been proliferative in the same physiologic sense. The terms "atrophic," "early proliferative with atrophy," and "late proliferative with atrophy" also were used. The source of the estrogenic stimulus to endometrial proliferation was considered to be extraovarian.

In the specimens of endometrium classified as atrophic there was a single layer of surface epithelium with a subjacent thin layer of stroma in which there were one or two and sometimes no glands per low-power microscopic field. The stroma was not always loose and in some instances was extremely dense. Several sections of atrophic endometrium revealed no glands that resembled those of proliferative endometrium but rather glands that resembled subbasal glands, small and apparently nonfunctioning. Atrophic endometrium was found in the

uteri of those women who, as far as could be determined from the menstrual history, had passed through the menopause in a normal fashion.

The endometrium classified as either early proliferative with atrophy or late proliferative with atrophy presented the typical picture of atrophy per several low-power microscopic fields. In other fields there also was a resemblance to the typical early or late proliferative endometrium, as described by Herrell and Broders (Figs. 1, 2, and 3).

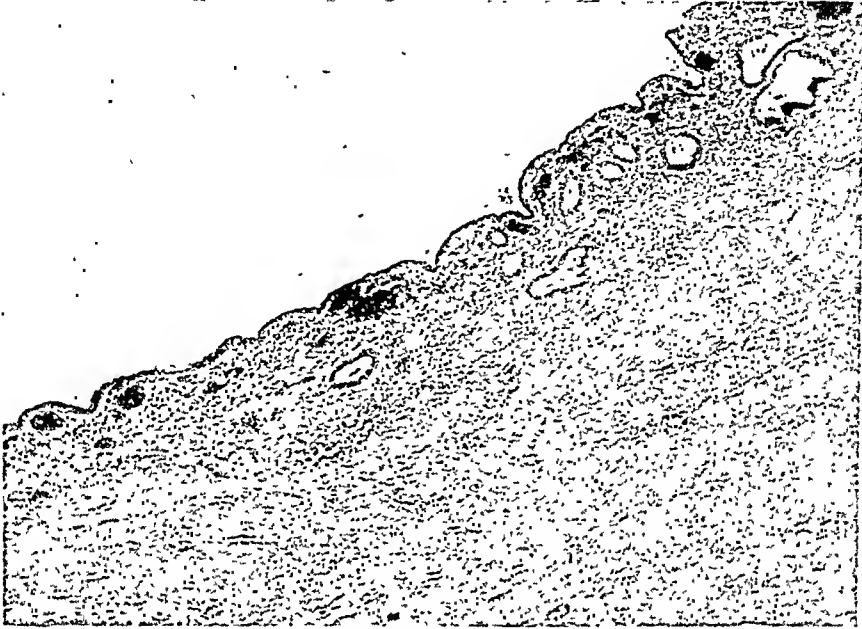


Fig. 2.—Early proliferative endometrium with atrophy. Section reveals atrophic endometrium on left of field and characteristic early proliferative endometrium on right of field ($\times 45$).



Fig. 3.—Late proliferative endometrium with atrophy. Section reveals atrophic endometrium in right portion of field together with late proliferative endometrium in left portion of field ($\times 22$).

A study was made of cystic change, accumulation of secretion, density of stroma, subbasal glands, and sclerosis of arteries and arterioles. These findings were graded on the basis of 1 to 4 per uniform field of microscopic magnification, grade 1 representing the minimal amount and grade 4 the maximal amount of

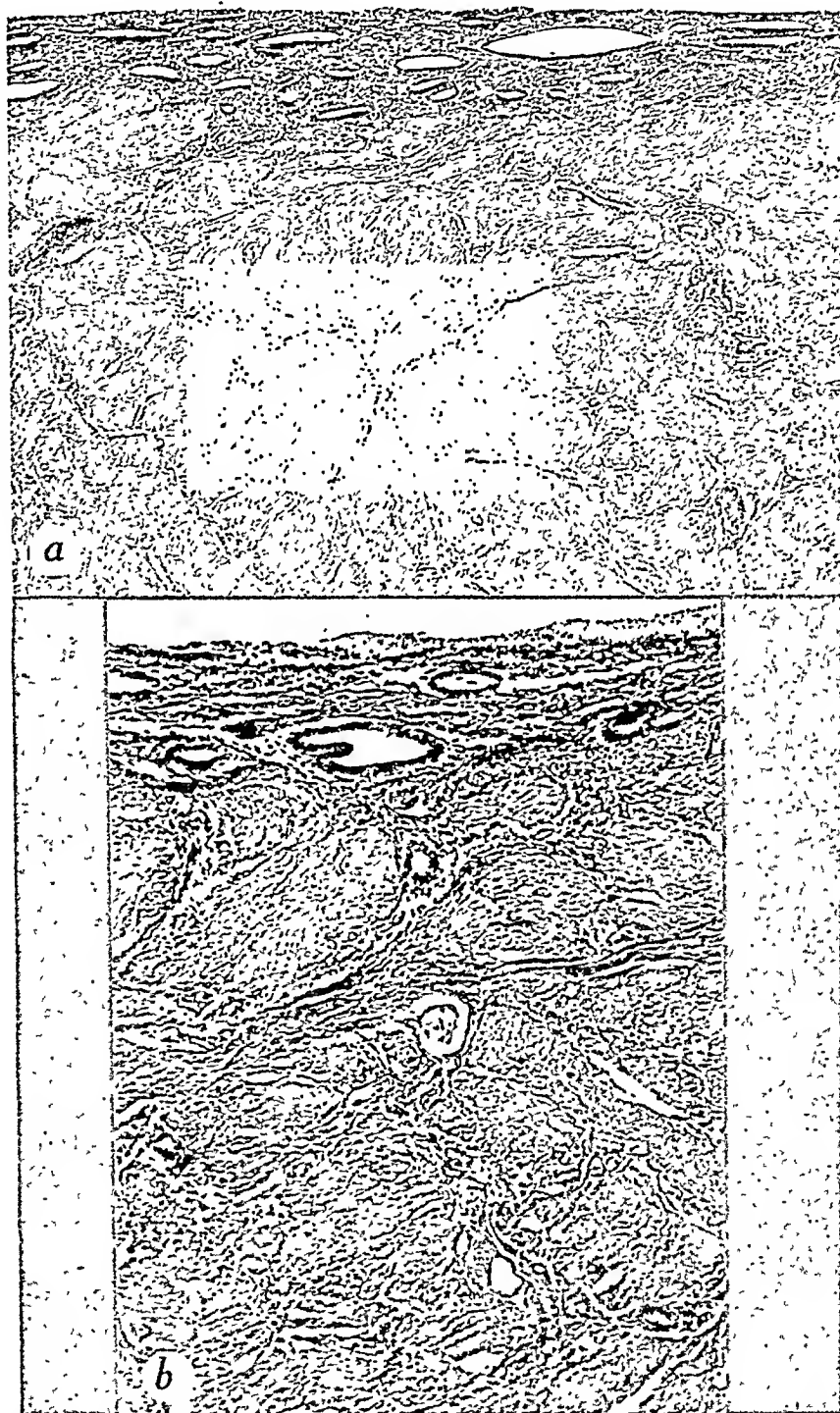


Fig. 4.—Subbasal glands, grade 1. *a*, Section reveals a few scattered subbasal glands in the lower portion of the endometrium with an occasional subbasal gland in the uppermost portion of the myometrium ($\times 45$); *b*, section reveals one subbasal gland just beneath the endometrium in the uppermost portion of the myometrium ($\times 100$, higher magnification of *a*).

such change. In classifying the cystic changes, preference for the concept that the endometrium was either early or late proliferative with cystic change was held. The gradation of 1 to 4 was made on the basis of size and number of cystic glands.



Fig. 5.—Subbasal glands, grade 2. Section reveals four subbasal glands just beneath the endometrium in the uppermost portion of the myometrium ($\times 75$).



Fig. 6.—Subbasal glands, grade 3. Section reveals numerous subbasal glands deep in the myometrium but in continuity with other subbasal glands reaching up to the myometrium ($\times 45$).

The gradation of accumulation of secretion depended on the number of cystic glands containing such secretion. The nature of this secretion, which stained light purple with hematoxylin, was not investigated but it seems probable that it was mucus. Its presence in the endometrial glands gave them the

appearance of endocervical glands and apparently indicated loss of function. Although the grade of cystic change roughly paralleled the degree of accumulation of secretion, it did not invariably do so. Thus, an endometrium with grade 4 cystic change but with only grade 1 secretion might be found.

The grading of the stroma on the basis of its density was made in a qualitative rather than a quantitative sense. In other words, no precise count of the number of stromal cells per unit area was made but rather an impression was gained by comparing the various specimens under the same power of microscopic magnification. As has been reported by many investigators, the stromal cells fell into two more or less well-defined groups: namely, (1) cells resembling small lymphocytes, and (2) cells somewhat larger with pale cytoplasm and large oval-shaped, dark-staining nuclei. The decidua-like or pseudodecidual changes of the latter type of stromal cell, in which they assume an epithelioid cell appearance, were not found, probably due to the fact that no specimen which exactly resembled the differentiative type of endometrium was found.

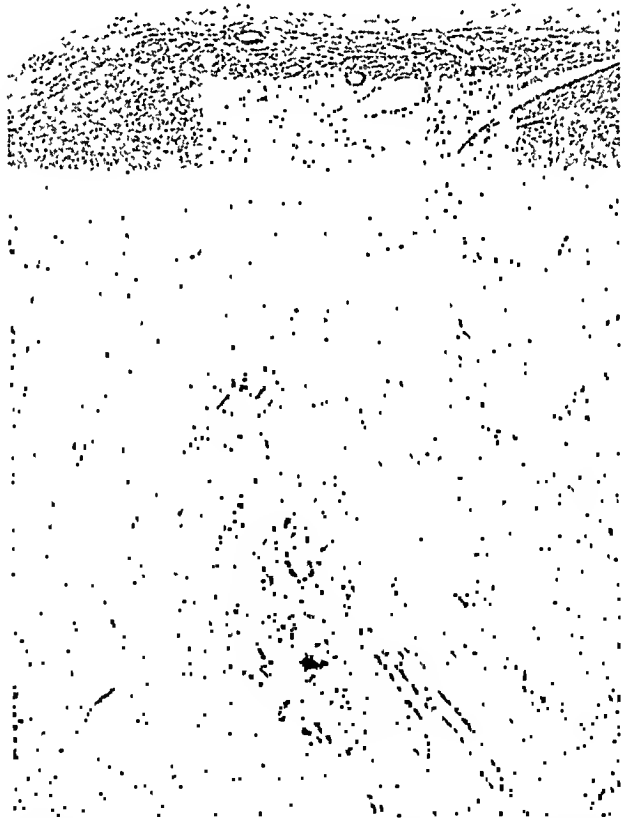


Fig. 7.—Subbasal glands, grade 4. Section reveals a group of subbasal and endometrial glands deep in the myometrium and completely isolated from the endometrium, a condition of so-called "adenomyosis" ($\times 40$).

The subbasal glands were graded on the basis of their number per low-power field and also on their distance beneath the surface epithelium. When the tissue was graded 4, the glands were well down into, and surrounded by, the myometrium. Thus they seemed similar to glands found in cases of adenomyosis. Since it was not the purpose of this study to go into the problem of adenomyosis

in detail, the extent of involvement of the subbasal glands merely was noted and classified so that the frequency of occurrence in the adenocarcinomatous and nonadenocarcinomatous uteri could be compared. Examples of the various grades of involvement of the subbasal glands are given in Figs. 4 to 7.

In grading the sclerosis of the arteries and arterioles, those specimens in which calcium deposition was seen were graded 4.

An estimation of the general thickness of the endometrium in each case was made by averaging, with reference to three sections of tissue, the fractions of the diameter of a low-power microscopic field which was occupied by endometrium. The same degree of magnification, of course, was used throughout the study in order to obtain an accurate comparison in the adenocarcinomatous and nonadenocarcinomatous uteri.

Comment and Results

As has been observed by many investigators, postmenopausal bleeding or spotting was the chief symptom in the vast majority of cases of adenocarcinoma of the corpus uteri. This symptom occurred in 70 of the 86 cases. In 15 cases there was bloody leucorrhea. Bleeding was absent in only one case.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed in 74 cases, vaginal hysterectomy in 7, Wertheim's hysterectomy in 4, and subtotal abdominal hysterectomy with bilateral salpingo-oophorectomy in one. In all cases, diagnostic dilatation and curettage preceded surgical removal of the uterus.

In 21 of the 86 cases of adenocarcinoma, the lesion was graded 1; in 23 it was graded 2; in 15, graded 3; and in 27, graded 4, according to Broders' method (Table I).

The number and percentage of cases in which the various types of endometrium were found, as well as the total number of cases of early proliferative endometrium with or without associated atrophy, of late proliferative endometrium with or without associated atrophy, and of atrophic endometrium with or without proliferation, also are shown in Table I. The total number of cases that showed early proliferative, late proliferative, or atrophic changes appear in the third column under each heading; obviously, due to the fact that some cases appear in more than one column, the total number of cases and the total percentage are not 86 cases and 100 per cent, respectively. The fact should be re-emphasized that the terms "early proliferative" and "late proliferative," in order to be entirely accurate, should be qualified by the statement that such endometrium corresponds in histologic appearance to early proliferative or late proliferative endometrium, as the case may be, but that it may not be proliferative in the same physiologic sense.

The important deduction to be made from the study of 86 cases of adenocarcinoma of the corpus uteri is that the number of cases of each type of endometrium does not vary appreciably with the grade of malignancy. Of the 21 cases of grade 1 adenocarcinoma and the 23 cases of grade 2 adenocarcinoma, the greatest percentage of cases had early proliferative endometrium, whereas the greatest percentage of the grade 3 (15 cases) and the grade 4 (27 cases)

TABLE II. COMPARISON OF FINDINGS IN ADENOCARCINOMATOUS AND NONADENOCARCINOMATOUS CORPUS UTERI

	GRADE 1		GRADE 2		GRADE 3		GRADE 4		NONE	
	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*	CASES	PER CENT*
ADENOCARCINOMATOUS UTERI (86 cases)										
<i>Grade 1 (21 cases)</i>										
Cystic change	2	9.5	5	23.8	5	23.8			9	42.9
Accumulation of secretion	2	9.5	7	33.3	3	14.3			9	42.9
Density of stroma	2	9.5	10	47.6	9	42.9				
Subbasal glands	5	23.8	2	9.5	3	14.3	3	14.3	8	38.0
Sclerosis of arteries and arterioles	8	38.0	5	23.8	7	33.3	1	4.8		
<i>Grade 2 (23 cases)</i>										
Cystic change	7	30.4	2	8.7	3	13.0	1	4.4	10	43.4
Accumulation of secretion	6	26.0	5	21.7	1	4.4			11	47.8
Density of stroma	2	8.7	9	39.0	9	39.0	3	13.0		
Subbasal glands	6	26.0	3	13.0	4	17.4			10	43.4
Sclerosis of arteries and arterioles	5	21.7	10	43.4	4	17.4	3	13.0	1	4.4
<i>Grade 3 (15 cases)</i>										
Cystic change	3	20.0	5	33.3	2	13.4			5	33.3
Accumulation of secretion	4	26.8	4	26.8	1	6.7			6	40.0
Density of stroma	2	13.4	9	60.0	4	26.8				
Subbasal glands	7	46.7	1	6.7	3	20.0	2	13.4	2	13.4
Sclerosis of arteries and arterioles	3	20.0	4	26.8	7	46.7	1	6.7		
<i>Grade 4 (27 cases)</i>										
Cystic change	7	25.9	3	11.1	3	11.1	2	7.4	12	44.4
Accumulation of secretion	5	18.5	6	22.2	2	7.4	2	7.4	12	44.4
Density of stroma	6	22.2	11	40.7	10	37.0				
Subbasal glands	7	25.9	8	29.6	1	3.7	3	11.1	8	29.6
Sclerosis of arteries and arterioles	2	7.4	11	40.7	13	48.1			1	3.7
ADENOCARCINOMA, ALL GRADES (86 cases)										
Cystic change	19	22.1	15	17.4	13	15.1	3	3.5	36	41.8
Accumulation of secretion	17	19.8	22	25.6	7	8.1	2	2.3	38	44.1
Density of stroma	12	14.0	39	45.3	32	37.2	3	3.5		
Subbasal glands	25	29.1	14	16.3	11	12.8	8	9.2	28	32.6
Sclerosis of arteries and arterioles	18	20.9	30	34.8	31	36.0	5	5.8	2	2.3
NONADENOCARCINOMATOUS UTERI (150 cases) (100 surgical; 50 necropsy)										
<i>Cystic change</i>										
Surgical	43		20		10		1		26	
Necropsy	11		19		12		4		4	
Total	54	36.0	39	26.0	22	14.7	5	3.3	30	20.0
<i>Accumulation of secretion</i>										
Surgical	31		5		1		1		62	
Necropsy	19		7		4		1		19	
Total	50	33.3	12	8.0	5	3.3	2	1.3	81	54.0
<i>Density of stroma</i>										
Surgical	21		34		24		21			
Necropsy	9		18		14		9			
Total	30	20.0	52	34.6	38	25.3	30	20.0		
<i>Subbasal glands</i>										
Surgical	14		22		14		16		34	
Necropsy	5		5		11		2		27	
Total	19	12.7	27	18.0	25	16.7	18	12.0	61	40.6
<i>Sclerosis of arteries and arterioles</i>										
Surgical	38		46		14				2	
Necropsy	24		7		4		5		10	
Total	62	41.3	53	35.3	18	12.0	5	3.3	12	8.0

*In group of adenocarcinomatous uteri, grades 1, 2, 3 and 4, the percentage figures represent per cent of cases for respective grade of adenocarcinoma; in group of adenocarcinomatous uteri, all grades, the percentage figures represent per cent of 86 cases; in group of nonadenocarcinomatous uteri, the percentage figures represent per cent of 150 cases.

had late proliferative endometrium. However, when the cases of early proliferative endometrium are added to the cases of late proliferative endometrium to obtain the total cases of proliferative endometrium, whether late or early, no appreciable variation in percentage with the grade of malignancy is evident. The percentage of cases of proliferative endometrium, grade 1, was 61.9; grade 2, 56.5; grade 3, 60.0, and grade 4, 55.5. Likewise, there was no noteworthy variation in the percentage of cases of atrophic endometrium, irrespective of the grade of adenocarcinoma. The percentage of cases of atrophic endometrium, grade 1, was 9.5; grade 2, 21.7; grade 3, 13.4; and grade 4, 14.8.

No instance of endometrium corresponding exactly to differentiative endometrium was found. There were two cases that had some features similar to differentiative endometrium but these were finally classified as corresponding to the late proliferative variety.

A similar histologic examination was made of the 150 uteri that were not involved by adenocarcinoma (Table I), and a comparison of the totals in the two groups of cases shows no appreciable difference in the percentage of cases of each type of endometrium. In fact, the percentages run consistently similar in the two groups of cases. One noteworthy discrepancy exists in the cases of atrophic endometrium, the percentage of this condition in adenocarcinomatous uteri being 41.8 as compared with 16 in nonadenocarcinomatous uteri. This is suggestive, although indirect, evidence against the concept that hypertrophy predisposes to the development of carcinoma. In fact, it seems to indicate that corporal carcinoma tends to occur more frequently in uteri in which there are atrophic changes in the endometrium than in those in which there are not.

The cystic changes, accumulation of secretion, density of stroma, subbasal glands and sclerosis of arteries and arterioles for both the adenocarcinomatous and nonadenocarcinomatous cases are graded in Table II. The percentage of cases with cystic change and accumulation of secretion graded 3 and 4 is roughly the same in the two groups. Thus, this study does not substantiate the theory that this type of endometrium predisposes to uterine malignancy. It also may be significant that in the adenocarcinomatous group, 41.8 per cent of cases showed no cystic changes, whereas only 20 per cent of the nonadenocarcinomatous group had no cystic changes. The percentages of stromal density, grade 1 and grade 2, and of grade 3 and grade 4 are roughly the same in the two groups. The fact that there was no consistent difference in the presence of subbasal glands would tend to indicate that they have no causal relationship to uterine carcinoma. The same may be said in so far as the degree of sclerosis of arteries and arterioles in the subendometrial tissues and muscularis is concerned.

There was virtually no difference in the average thickness of the endometrium in the two groups. The average thickness measured in fractions of the diameter of a low-power microscopic field was as follows: adenocarcinomatous uteri, 0.3 to 0.36; nonadenocarcinomatous uteri, 0.3 to 0.4; surgical cases 0.36, necropsy cases 0.3.

A detailed study of adenomatous polypi was not made because in all cases, as previously mentioned, dilatation and curettage had been performed. Thus, some of the existing polypi undoubtedly had been removed. Four uteri in which

TABLE III. DATA CONCERNING 236 WOMEN IN THE POSTMENOPAUSAL STATE

	ADENO- CARCINOMATOUS UTERI	NONADENOCARCINOMATOUS UTERI	
		OPERATION FOR CONDITION OTHER THAN CARCINOMA	ROUTINE NECROPSY
Cases	86	100	50
Age, years	39 to 80	49 to 78	50 to 93
Average age, years	53	61	63
Time since menopause	2 mo. to 25 yr.	1 mo. to 30 yr.	1 mo. to 43 yr.
Average time since menopause	7 yr.	12 yr.	14 yr.
Para 0, gravida 0	23	29	18
Average gravidity and parity	3-3	3-3	3-3
<i>Associated pathologic condition</i>			
No cysts in ovaries	33	36	20
Fibromyoma			
Single	11	14	3
Multiple	19	23	9
Adenomatous polyp			
Single	1	8	7
Multiple	3	14	3
Adenomyoma	2	5	2 (1 in round ligament)
Endometrioma	1	2 (ovary)	1 (ovary)
Carcinoma showing regions of squamous-cell metaplasia	3		
Carcinoma simulating			
Sarcoma	1		
Squamous-cell epithelioma	1		
Cervix, carcinoma grade 2 to 4	1		
Chronic cervicitis	31	66	40
Cystic cervicitis	18	28	6
Cystic adenomatous polyp of cervix	3	6	4
Cysts of Morgagni			
Single	1	2	1
Multiple		3	1
Intracystic carcinoma (ovary)		2	1 (small)
Metastatic carcinoma (ovaries)		1	1 (small)
Fibroma (ovaries)	3	2	3
Intracystic fibroma (ovary)			1
Multilocular cyst (ovary)		1	1
Cystic oophoritis (bilateral)	7	11	6
Chronic oophoritis with papillary cystadenoma (left ovary)	1		
Chronic oophoritis			
Right	2		
Bilateral	7	12	5
Dermoid cyst (left ovary) and atrophy (right ovary)	1		
Bilateral atrophic ovaries	49	82	42
Adenocarcinoma, grade 4 (one ovary), and bilateral ovarian cystadenomata	1		
Metastatic nodule on right ovary with chronic oophoritis on left ovary	1		
Luteinization (ovaries)	4	9	5 (no cysts)
Corpus luteum			1 (aged 63 yr.; 25 yr. past meno- pause)
Hydrosalpinx			
Single (with other chronic salpingitis)	1	4	3
Bilateral	2	6	3
Metastatic adenocarcinoma (right tube) and chronic salpingitis (left tube)	1		
Bilateral chronic salpingitis	58	72	38
Atrophic tubes	11	14	6
Multiple carcinomas in uterus	1		

polypi were present were found in the 86 cases of adenocarcinoma, an incidence of 4.7 per cent (Table III). Twenty-two polypi were found in the 100 cases in which the uteri had been removed for other conditions, an incidence of 22 per cent. Ten were found in the 50 cases in which necropsy had been performed and in which no malignant lesion was present, an incidence of 20 per cent. These figures suggest that polypi occur with considerably less frequency in uteri in which adenocarcinoma is present than in those without adenocarcinoma. This seems to be incompatible with the generally held conception that uterine polypi are precarcinomatous; however, the figures are merely suggestive.

Additional information concerning the 236 cases studied, including the associated pathologic conditions found on gross examination of the specimens, is shown in Table III. These findings are included merely for completeness.

Summary and Conclusions

The material studied consisted of postmenopausal uteri in 236 cases. In 86 of these cases the uterus had been removed because of adenocarcinoma, and in 100 cases it had been removed for other reasons. In 50 cases routine necropsy had been performed.

In the group of 86 women who had adenocarcinoma of the corpus uteri, all but one had had vaginal bleeding or spotting as a presenting complaint.

In the 86 cases of adenocarcinomatous uteri there was no appreciable variation in the percentage of cases with proliferative endometrium, whether early or late, or in the percentage of cases with atrophic endometrium, according to the grade of malignancy.

There was no appreciable difference in the percentage of cases of any given type of endometrium in adenocarcinomatous uteri as compared with nonadenocarcinomatous uteri, except with regard to atrophic endometrium. Thus, 41.8 per cent of cases of uteri with malignancy showed atrophic endometrium and only 16 per cent of cases of uteri without malignancy showed atrophic endometrium. This suggests that adenocarcinoma of the uterine corpus is more likely to occur in cases in which there is atrophy of the endometrium than in cases in which there is no atrophy.

Two of the 86 cases of adenocarcinomatous uteri and three of the 150 cases of nonadenocarcinomatous uteri presented some features similar to those found in early differentiative endometrium but since they were not entirely the same the endometrium was classified as late proliferative.

The percentage of cases with grade 3 and 4 cystic change and with grade 3 and 4 accumulation of secretion was roughly the same in the two groups of cases. Approximately 42 per cent of adenocarcinomatous uteri showed no cystic changes, whereas 20 per cent of nonadenocarcinomatous uteri showed no cystic changes. This lends evidence contrary to the view that the "Swiss-cheese endometrium" of Novak has any features predisposing to the development of carcinoma.

There was no consistent difference or variation of cystic change, accumulation of secretion in the glands, density of the stroma in and beneath the endometrial epithelium, involvement of the subbasal glands or sclerosis of the arteries

and arterioles, according to the grade of adenocarcinoma. In 28 of the 86 cases no subbasal glands were found. Thus, subbasal glands seem to have no causal relationship to adenocarcinoma of the uterus.

There was virtually no difference in average thickness of endometrium in adenocarcinomatous uteri as compared with nonadenocarcinomatous uteri.

The incidence of endometrial polypi in uteri without adenocarcinoma was roughly eight times greater than their incidence in uteri containing adenocarcinoma. However, previous curettage in all cases of malignancy might be partially responsible for the variation.

In general, it may be concluded from this comparison of adenocarcinomatous and nonadenocarcinomatous uteri removed from women who had passed the menopause, that the uninvolved portion of endometrium in the former group was in no demonstrable way different from that of the endometrium in the latter group except that atrophic endometrium was found more often in adenocarcinomatous uteri than in nonadenocarcinomatous uteri, while endometrial polypi were found more often in nonadenocarcinomatous uteri.

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THE ANOVULATORY CYCLE AND MENSTRUATION

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THE concept of an "anovulatory cycle" is the product of anatomie and biologic investigations, which are not only of interest, but of practical importance, to the gynecologist. The classical studies of Corner^{5, 6} and Hartman¹² were the first in the field and are too well known to require detailed restatement. Anovulatory bleeding has been termed menstruation due to some similarity of the former to the latter, but I want to show that they differ in essential details. Among the similarities is the recurrent nature of both, particularly in the monkey. In this regard there could be no objection to the term anovulatory cycle, since proliferative changes in the ovary and the endometrium pass into regression, and return to their original state. This is not necessarily rhythmical since the term rhythmical denotes a regularity in the time of recurrence at least approximating that of menstruation in the normal healthy woman.

What Is the Anovulatory Cycle?

Similarities and Differences With Menstruation.—Anovulatory bleeding represents a premature interruption of the menstrual cycle. Does the interruption of the cycle occur only at the time when the rupture of the follicle should take place, or can the interruption occur at any time before or after the rupture? This question is important since, at the time of anovulatory bleeding, the endometrium of monkeys shows various degrees of proliferation, as is evident in the pictures appearing in the works of Corner and others.

A brief summary of the known changes which occur in anovulatory bleeding is as follows: The follicle regresses while the endometrium is still in the proliferation phase. Anovulation occurs with the shedding of a thin necrotic superficial layer of the endometrium. These two features, the involution of the ripened follicle and of the proliferating endometrium, clearly belong to the basic picture of the anovulatory cycle. The condition of the egg cell is unknown.

Not only is the incidence of anovulatory bleeding in the human unknown, but too little is known of the extent of the follicular development, and the details of its regression in anovulatory bleeding. This is particularly true if one requires histologic control of the ovaries for diagnosis. Some authors have described anovulatory bleeding on endometrial findings in young girls and sterile women. Others using large quantities of material for investigation (R. Schroeder,²¹ R. Meyer),²⁰ have also reported the frequent discovery of functionless endometrium in young girls and women who reported regular bleeding. In the majority of these cases, however, the endometrium was

either poorly developed or even atrophic. Only occasionally was there sufficient response to justify a diagnosis of normal proliferation phase.

Under any circumstances, it would appear that the similarity of function between the monkey during periods of anovulatory bleeding, and the girl at puberty, has been overemphasized. Gambarow¹⁰ concluded from his studies that it is doubtful if it occurs at all. The ability of young girls to conceive has been studied in large numbers in Russia, and he was able to report on 22 cases in which conception occurred in girls of thirteen to fifteen years of age and before menstruation began. It is remarkable that pregnancies may occur in one to three months after the beginning of intercourse and before the onset of menstruation. These findings confirm those reported from India where marriage at twelve years of age is not uncommon.

Immediately following the surprising discovery of the process of anovulatory bleeding, much emphasis was placed on its rhythmic recurrence; but, as a matter of fact, this is very rarely the case. Allen¹ describes as a peculiarity the regular recurrence of such bleeding eight times in a monkey, but endometrial hyperplasia may show an equal regularity of bleeding episodes, and there is no doubt that this is a pathologic condition. It has the same hormonal background as anovulatory bleeding except that in the case of hyperplasia, the effect is continued over a longer period of time. Since some similarities exist between anovulatory and ovulatory bleedings, the bleeding and necrosis with shedding of the endometrium, added to the rough regularity of recurrence, soon gave rise to the term "anovulatory menstruation." During the summer time the anovulatory cycle in monkeys in captivity is a common occurrence. Joachimovits¹³ states, on the basis of his studies, that anovulatory bleeding is exceptional in monkeys in the tropics. So it seems to be clear that captivity acts like domestication on the regularity of the anovulatory cycle.

Interruption in early premenstrual endometrium is described by Corner⁶ (1939) in a monkey after an operation. But this also happens in women, as Bartelmez^{3,a} has pointed out. I can illustrate such a case in a 25-year-old woman. The menses were formerly regular. For one year following an abortion, the menses were irregular. A curettage was done on the second day of bleeding, which started eighteen days after the beginning of the last period. As shown in Fig. 1, the surface everywhere had been cast off; the remaining endometrium was in decay. The glands were moderately tortuous, and the epithelium contained glycogen in the upper parts of the cells.

I believe that this case constitutes a premature interruption of the cycle in the early secretory phase.

Such bleedings may also occur in humans during the menarche, lactation, and climacterium, as some observers maintain, but mostly the histologic picture is so irregular that it does not resemble the normal proliferative phase. If these bleedings appeared during the active sexual life of women, they would be abnormal disturbances.

The definition of anovulatory bleeding as recurrent bleeding from the shedding of a proliferated endometrium suggests that it occurs just before the time when ovulation might be expected, and so is associated with manifestations

of estrus. This at once suggests the similarity to the regression which occurs at the end of estrus in the lower animals when copulation has not taken place. Even in those animals where estrus is associated with bleeding, no reasonable basis exists for identifying it with menstruation. They are, rather, two different kinds of regression as is acknowledged generally now. In the primate, the cycle normally continues after estrus as a special pregravid phase, while in lower animals it reaches an abrupt end after estrus, and is thus comparable to anovulatory bleeding.

If estrus bleeding and menstruation in different animals are not the same, then anovulatory bleeding and menstruation when both happen in primates, are not comparable either. In both estrus bleeding and anovulatory bleeding, the pregravid phase of the primate is missing.



Fig. 1.

Phylogenesis and Menstrual Cycle

Allen, Hisaw, and Gardner,² in comparing the estrus cycle in the lower animals with the menstrual cycle in the primates, state: "Why this degenerative phase is accompanied by menstruation in many primates is still unknown." How the evolution of these functions have come about is a fundamental problem in phylogenesis and biogenesis.

Certain features of the problem may, however, be worth discussing. At first glance it might be thought that this had little to do with the problem at hand, but I believe that short consideration of the general background of menstruation may establish a broader concept, which will be useful in discussing the relation between menstruation and anovulatory bleeding.

First of all, it may be stated that menstruation must not be considered apart from its relation to the cycle and to the whole sex function. Only a few decades ago, the interest of the gynecologist was focused upon the process of menstruation as though it were the most important event in the natural history of women. At that time a distinction had been drawn between a true and a false corpus luteum. It is now a matter of general knowledge that there is but one corpus luteum, and that it is either living and functioning

in the pregravid phase and in pregnancy, or dying and functionless during menstruation and post partum. In this regard, it was even difficult to get general acceptance of the fact that the masses of stainable lipids in the luteal cells during and after menstruation did not represent function but were actually nothing but decomposition products. At the present time there is general agreement that the cycle changes, in both the ovary and endometrium are in every respect a preparation for the anticipated pregnancy. It appears to be still necessary, however, to point out that menstruation should not be considered apart from the other phases of the pregravid changes of the cycle.

The designation of menstruation as an "abortion" now may serve its purpose in making more plausible the explanation of the difference in mechanism between menstruation and the simpler forms of involution in the lower animals. In a general way, though not in all details, an explanation may be had by referring to differences in the relation between placental and maternal tissue.

The placentas of different species vary widely. Various terms have been applied to describe these placentae verae and semiplacentae or apposed and conjoined placentas. Grosser¹¹ has suggested a more detailed classification. These are, in order of increasing degrees of contact and invasion, placentae epitheliochorialis, syndesmochorialis, endotheliochorialis and hemochorialis. These describe the degree of connection between the placental chorion and the more superficial or deeper parts of the uterine tissue, namely, the epithelium, connective tissue, endothelium of the vessels, and maternal blood. It is easy to understand that the endometrium in the preparation for pregnancy must progress to a stage adequate for the varying degrees of aggressiveness of the chorion specific to every species. This involves special histologic and chemical preparations of the maternal tissue needed for the specific type of nutritional requirement of the ovum. Indeed, even before fertilization, the endometrium reacts by pregravid changes, specific for each species. The differences in these changes are particularly evident when one compares the primate with some lower animals.

In the primate, the decidua and its vessels are developed in a remarkable degree, in order to satisfy the angiotactic demands of the fetal chorion which, in this case, will form a hemochorial placenta.

The changes of the human endometrium pass in the second half of the cycle to those which satisfy the requirements of implantation and pregnancy. The connective tissue begins to show decidual change first in the neighborhood of the vessels and later more diffusely. The endothelium of the capillaries in the superficial layer of the endometrium are delicate and fragile. The musculature is quite loose and softened. These changes advance during early pregnancy.

In his excellent description of a normal human ovum in a very early stage, Brewer⁴ pointed out that in the endometrium the vascular phenomena of vasoconstriction and dilatation, superficial ischemic necrosis, superficial venous congestion, extravasation, and reduced arterial flow are similar to those described

for menstruation. These vascular phenomena serve to prepare and maintain a site suitable for implantation and growth of the young ovum. The most interesting of these phenomena, carefully described by Brewer,⁴ is the ischemic necrosis in the superficial layer of the endometrium. This is independent of the direct influence of the trophoblast, and is similar in every detail to the ischemic necrosis seen in the endometrium during menstruation. In this connection it might be pointed out that, not only all other pregravid changes of the endometrium of the primate, but also the vascular reactions immediately preceding menstruation, are the same as in early stages of pregnancy.

There is evidence that the histologic changes in the endometrium in preparation for pregnancy correspond to the specific requirements of the ovum of the given species. Further, in some species the endometrium undergoes changes to accommodate itself to the gross form of the ovum. These changes precede nidation. All of this has been but briefly mentioned, but it would seem to explain satisfactorily the various types of involution of the endometrium in lower animals and primates, if fertilization does not occur. It also points again to the fact that menstruation should not be forced out of its natural associations, but should be described as the breaking down of a primate endometrium which has undergone changes, and reached a stage corresponding histologically and hormonally to that of an early pregnancy.

Recently some authors have greatly emphasized the constriction of the coiled arteries and resultant ischemia which occurs in the endometrium in connection with both anovulatory and menstrual bleeding. Markee¹⁴⁻¹⁹ was able to transplant endometrium into the anterior chamber of the eye and to observe the ischemia which preceded both menstrual and anovulatory shedding. This demonstration was said to remove the last doubt that anovulatory bleeding could be anything but a normal process. It must be pointed out, however, that the appearance of ischemia is a preliminary disturbance in almost all forms of necrosis, both pathologic and experimental.

Daron⁷ was able to show a significant difference in the coiled arteries of the endometrium of the ovulatory and anovulatory cycle. In the *Macaca rhesus* monkey, the coiled arteries continue to differentiate during the pregravid phase while the endometrium increases only slightly in thickness during this time. In the first half of the cycle, the endometrium increases rapidly in thickness while the arteries differentiate slowly. With menstruation, the arteries at the surface are completely occluded. The deficient arterial development in the anovulatory cycle indicates that menstruation is not imminent. In anovulatory bleeding, the coiled arteries are not at the surface and their terminal arterioles are still intact even though some tissue may have been lost.

This is not the place to abstract Daron's important work at length. Only one finding will be mentioned. He was able to demonstrate that the arteries on the nineteenth and twenty-first days of the anovulatory cycle did not show the degree of development achieved by the sixteenth day of the ovulatory cycle. This can be considered as retardation of the development in the anovulatory cycle, which will not allow it to appear as a normal process.

There is another difference between the two processes, which is brought about by differences in hormonal effects. Anovulatory bleeding is caused by a destruction of a nonsecretory endometrium. In true menstruation only that part of the endometrium which has undergone secretion phase changes becomes necrotic, while the nonfunctioning basalis is retained. The most important morphologic differences between ovulatory menstruation and anovulatory bleeding have been pointed out. A comparison shows that they have little in common.

It is also evident that the morphologic differences correspond well to the functional differences. The pregravid changes of the endometrium may be considered as the most important feature of the cycle. The excretion from the endometrium of arsenic, iodine, phosphorus, calcium, magnesium, and sulfur gives to menstruation a secondary, but important, significance as a channel for the removal of toxic substances (L. Fränkel,⁹ O. Grosser,¹¹ R. Schroeder²¹). This is not reproduced in anovulatory bleeding.

Experimental Research

Now are there any experimental results regarding the mechanism of hormonal regulation in anovulatory bleeding, which might justify placing it on a par with menstruation? From his hormonal experiments, Corner draws the following conclusions: "In the normal cycle the uterus will not bleed during the first half (follicular phase), because the ovaries are furnishing estrin. It will not bleed during the second half of the cycle (corpus luteum phase), because the corpus luteum is furnishing progesterone. The production of estrin in all probability continues. By an assumption, however, the corpus luteum undergoes retrogression, the animal is suddenly deprived of the action of both estrin and progesterone, and the endometrium breaks down. Ovulatory menstruation is thus a special case of estrin-deprivation bleeding."

This ingenious hypothesis does not find agreement with other experimental work. Engle,⁸ in quoting the hypothesis of Corner, makes some remarks which are based on the findings of Markee. If, during the pregravid phase, progesterone merely prevents the protective function of the estrogen as Corner suggests, it also circumscribes the action to a period of twenty-four hours.

Engle pointed out that in both the normal ovulatory bleeding and anovulatory bleeding, the application of progesterone inhibits bleeding but estrogen does not. If any conclusion is to be drawn from this experiment, we should have to ask if the lack of progesterone enables the estrin to cause necrosis and bleeding. Reynolds states that continued injections of estrin as a maintenance dosage gives rise to occasional uterine bleeding. He concludes: "This betokens an inherent alteration in the sensitivity of the uterus to hormone under continued uniform stimulation." We might ask if this is the same way in which bleedings occur in hyperplasia, or are they caused by intermittent lack of estrin? It appears more reasonable that the withdrawal of either hormone permits conditions to develop within the vascular supply or the tissues of the endometrium

which lead to the phenomena of menstrual bleeding. Only the time of onset is different.

Smith and Engle²² showed that after the withdrawal of estrogen, bleeding did not appear if the estrogen were replaced by progesterone. After the withdrawal of progesterone, bleeding occurred and was not prevented by estrogen in large doses. This seems to verify the conception that menstruation is caused by the cessation of progesterone action on the endometrium.

According to Engle, the character and duration of the bleeding resulting from withdrawal of either hormone are the same, but the time interval for each is different: for estrogen, 9.2 days, with a range of 6 to 16 days; and after progesterone treatment cessation, 2.9 days, with a range of 2 to 4 days.

The longer duration of regression in the follicle is certainly at variance with the usual sudden regression of the corpus luteum. If one can apply the results obtained from experimental withdrawal of estrin to anovulatory bleeding, the conclusion would be reached that regression of the follicle has preceded the bleeding by an average of 9.2 days with a range of 5 to 6 days. This range is so great that we would expect to be able to find the different stages of follicle regression. Or is the experiment not comparable with the natural process?

The knowledge of hormone relationships, while incomplete, has advanced to the stage which justifies Corner's⁶ conclusion that the only possible explanation of natural menstruation is on the basis of the recurrent function and loss of function of the corpus luteum. This is in complete agreement with the observations and conclusions of R. Schroeder, R. Meyer, and others. There is no difference between Corner's opinion and ours as he seems to believe.

Conclusions

From the preceding, then, it seems clear that the results of both the histologic and hormonal investigation of anovulatory bleeding are still grossly incomplete. The findings do not yet agree well with the hypotheses. An objective consideration of the details of what is known of ovulatory and anovulatory bleeding leads to the conclusion that, although some similarities exist, the differences between the two are such as to exclude the propriety of considering them to be identical. It is scarcely necessary to present further evidence in support of the statement that a sharp line can be drawn between anovulatory bleeding and menstruation. The line separating them is clear, clearer even than between benignity and malignancy, or between physiologic and pathologic inflammation.

The limited definition of menstruation is essential for a proper perspective. In the absence of this, many technical difficulties arise. If one recognizes two types of menstruation, one must also describe two different premenstrual conditions.

Whether similarities justify the classification of ovulatory and anovulatory cycles under a common heading is another question. Both might be considered as abortive processes. The anovulatory cycle may be compared to the prepubertal interruption of the developing follicle without bleeding, while on the

other hand the cycle which ends with menstruation is more comparable to the abortion of an early pregnancy. These four types of abortive processes are determined by the death of the ovum. The difference between the abortion of the early pregnancy and the other three does not require further discussion, but one may point out the close histologic and hormonal relationships between the pregravid stage and the early pregnancy. This is the cardinal point from the gynecologist's point of view, as he will not fail to recognize the significance of the anovulatory cycle. It is important to keep clearly in mind the fact that the regular recurrence of bleeding does not necessarily signify menstruation. This is occasionally determined by the examination of curettage material. There is now every reason to believe that in the absence of another evident cause of sterility, the endometrium of these patients should be thoroughly examined before the anticipated bleeding.

For the gynecologist, the essential feature of the whole problem revolves about fertility. This is not only important to the woman concerned, as an individual physiologic process, but is a point of great biologic significance in the broad biology of perpetuated life.

It is in this broad field that the gynecologist acts as custodian. He must count on the relation of a true menstrual cycle and potential fertility. Only under these circumstances is there hope that the function of reproduction will be completed. This should be the thought of every gynecologist and should explain his objection to the use of the term menstruation for other processes. The term menstruation is not a meaningless word or a matter of opinion. It represents a function that carries the significance of a long historic background and has a scientifically determined, sharply circumscribed meaning, the goal of which is life.

The whole question, then, is not a simple academic argument, but represents the clashing of two thought processes. The biologist thinks in terms of etiology and the gynecologist in terms of ultimate ends.

Summary

The uterine bleeding, called anovulatory cycle, does not appear at a definite point in the cyclical changes of the follicle and the endometrium. Interruption of the cycle in either causes bleeding both in the early and in the late time of proliferative stage, and occasionally at any time in the luteal stage.

The similarities between true menstruation and the anovulatory cycle, namely, the ischemic necrosis and bleeding caused by the nonproduction of hormones, are superficial when compared with the fundamental differences. These latter are stipulated by the revolutionary hormonal, chemico-functional, and morphologic preparations of the endometrium for pregnancy. These preparations in the primate differ from those in the lower mammals, because they must be adapted to very different types of placentation. For this reason the regression of the endometrium when fertilization does not occur must necessarily also be fundamentally different, so that one cannot relate estrous bleeding to menstruation.

The fact that experimental biology and gynecology consider the problem from entirely different angles gives rise to their opposing positions. Because the gynecologist thinks in terms of ultimate ends, he will not allow the term menstruation to stand for anything except that which has been traditional. It is the symbol of sexual maturity and potential fertility. Without corpus luteum there can be no pregravid phase, without which there is no true menstruation.

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SELECTIVE TREATMENT OF ANTEPARTUM HEMORRHAGE*

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IF WE were to adopt any standard method for the treatment of all cases of antepartum hemorrhage, cesarean section would be the method of choice. To justify any other procedure the results must approach those of cesarean section. Where section is the routine treatment for these patients, it is probable that future pregnancies, particularly in the case of primiparas, will also be delivered by section. To the risk of the first operation, therefore, must be added the risk that the patient will undergo in future pregnancies. For many years on our service, hemorrhage in the last trimester of pregnancy has been treated in a selective manner. After consideration of all the circumstances of the case, the method of treatment for any particular patient is determined on the basis of obstetric judgment, and I present here the results of this policy over a period of seventeen years.

Hemorrhage remains one of the three great destroyers of women in childbirth, and is far less amenable to prophylactic measures than either puerperal sepsis or the toxemias of pregnancy. Postpartum hemorrhage can be minimized by proper prophylactic measures, but in antepartum hemorrhage, prophylaxis plays very little part, except in cases of toxemia with separation of the placenta. I wish to eliminate from discussion all bleeding previous to the last trimester and, for practical purposes, this leaves us with only placenta previa and accidental hemorrhage. Occasionally a patient is seen in labor who is having more bleeding than can be accounted for by normal show. We suspect that we are dealing with partial separation of a normally situated placenta or with placenta previa, yet the case may terminate spontaneously and successfully, and careful examination of the placenta fails to reveal which, if either, of these conditions was present. Some of these patients may have excessive show from the dilating cervix or due to separation of the membranes in the lower uterine segment. In others it may be due to a low-lying placenta or to a slight separation of a placenta that is normally situated. In this study an attempt has been made to eliminate all such cases. Diagnosis may be uncertain when the patient is first seen, but becomes clear as labor progresses, or after its termination.

The diagnosis between placenta previa and accidental hemorrhage is usually easily made. However, there are frequently cases where the differentiation between the two conditions will not be obvious when the patient is first seen. The bleeding may be slight, the patient in labor, and no evidence of toxemia may exist, yet the placenta may not be palpable at the lower uterine segment. It is obvious that there must be a site for placental attachment where it is impossible

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to say whether it is or is not normally situated. We do not believe that it is advisable to make any great effort to feel the placenta if it is not readily palpable at the internal os. X-ray examination, either by means of a cystogram or with the soft tissue technique, frequently gives information of value, but this is not always true.

Keeping in mind these occasional difficulties in diagnosis, Table I gives the classification of our cases of antepartum hemorrhage for the years 1928 to 1944 inclusive. From this table we have omitted cases of excessive show which we decided, after delivery, were neither placenta previa nor accidental hemorrhage.

TABLE I. 1928 TO 1944 INCLUSIVE

	NO.	%
Total deliveries	16,115	
Antepartum hemorrhage	330	2.04
Placenta previa	191	1.19
Accidental hemorrhage	139	0.87
Maternal mortality	9	2.7
Infant mortality	131	39.6

Let us now consider the 191 cases of placenta previa. The usual classification of this condition is marginal, lateral, and central placenta previa, to which is sometimes added low implantation of the placenta. There is no uniformity of interpretation of this classification, and we have recently discarded it for one we think more practical. We classify our cases as complete or incomplete. The latter are subdivided into those where the placenta is palpable and those where it is not palpable. All classifications are relative as to the stage in labor when they are described. A placenta that entirely covers the internal os at the beginning of cervical dilatation may have a considerable area of membrane present beyond the edges of the placenta when the cervix is half or more dilated. Similarly, a placenta which may not be palpated before effacement of the cervix may be readily reached later in labor. As our new classification commenced only in 1933, Table II covers only 1933 to 1944. Of these, 31 were complete and 106 incomplete. Of the latter, 71 were palpable and 35 nonpalpable at the time of examination.

TABLE II. CLASSIFICATION OF PLACENTA PREVIA, 1933 TO 1944

Complete	31 (plus 23, 1928 to 1933)
Incomplete	106 (plus 31, 1928 to 1933)
Palpable	71
Nonpalpable	35

The results of treatment of the whole 191 cases during the 17 years are exhibited in Tables III, IV, V, and VI.

It is worthy of note that three patients had spontaneous deliveries without severe loss of blood and without maternal death in spite of the fact that the placenta completely covered the internal os at the time of examination. In one instance the placenta was expelled in front of the child's head. None of these patients, however, was more than six and one-half months pregnant.

TABLE III. COMPLETE PLACENTA PREVIA, 1928 TO 1944

TREATMENT	NUMBER	DEATHS
Cesarean—classical	30	1 (intestinal obstruction)
—low	7	
—Porro	1	
Bag	4	
Version	8	1
Spontaneous	3	
Undelivered	1	1
	54	3 5.8%

TABLE IV. INCOMPLETE PLACENTA PREVIA, 1928 TO 1944

TREATMENT	NUMBER	DEATHS
Medical induction	7	
Rupture of membranes or spontaneous labor	77	
Vaginal packing	2	
Bag	28	
Internal version	12	2
External version	1	
Cesarean	10	
Classical	5	
Low	5	
	137	2 (1.46%)

In the 137 cases of placenta previa during 1933 to 1944, 69 had profuse bleeding from the start, and 68 had slight vaginal bleeding on one or more occasions. Information regarding the original bleeding in cases previous to 1933 is not available. Of the 68 cases which began with slight bleeding, 10 subsequently had profuse hemorrhage. Of these 68 cases, 9 were complete placenta previa and 59 were incomplete.

TABLE V. CASES BEGINNING WITH SLIGHT BLEEDING

Spontaneous	24
Bag	13
Section	17
Version	8 (1 death)
Forceps	3
Breech	1
Packing	2
	68 (1 death)

Table V shows the method of treatment of these 68 cases, from which it will be seen that slight bleeding as an original symptom does not determine the subsequent course of events. Seventeen of these patients, for instance, were treated by cesarean section. A practical problem in treatment is illustrated by this table. If a patient in the last trimester has slight painless bleeding it may or may not be due to placenta previa, but placenta previa should always be treated in a hospital. The patient, therefore, should be sent to the hospital before profuse bleeding has started. This will result in certain cases being sent to hospital who were having bleeding from the onset of labor without placenta previa, but no harm has been done, and those that really have placenta previa will be in the proper place for treatment.

TABLE VI. MATERNAL MORTALITY, PLACENTA PREVIA 1928 TO 1944

Total cases	191
Cesarean	1
Undelivered, 20 minutes after admission	1
Version	3
	<hr/> 5 (2.6%)

Table VI is an analysis of our maternal mortality in the whole series of 191 cases. One death followed classical cesarean section and was due to intestinal obstruction which was relieved by operation, but the patient did not survive. The second patient died twenty minutes after admission before anything except a transfusion could be carried out. The other three deaths all followed internal version. One patient was discharged from the hospital on the seventeenth day, having had a normal temperature for a week. She returned two days later with a phlebitis and died suddenly four days after her second admission from pulmonary embolism. The other two patients both died of hemorrhage in spite of repeated transfusions. In both of these cases the hemorrhage had been severe before admission and was still continuing, and it was thought that version was the only method of immediately controlling the bleeding.

TABLE VII. STILLBIRTHS AND NEONATAL DEATHS IN PLACENTA PREVIA, 1928 TO 1944

TREATMENT	NUMBER	DEATHS	PER CENT
Expectant	86	18	19
Cesarean	44	8	18
Bag	31	15	48
Internal version	20	12	60
External version	1	1	100
Packing	2	2	100
	<hr/> 184	<hr/> 56	29.6

Table VII is an analysis of the fetal mortality when various methods of treatment were carried out. It will be seen that expectant treatment and cesarean section have by far the lowest fetal death rate. Those cases treated expectantly are the ones with the lesser degree of hemorrhage; many patients are already in labor and no further treatment becomes necessary during the course of labor. Cases treated by cesarean section in some instances had profuse bleeding, in other cases the operation was done because of complete placenta previa, and usually the patient was not in labor.

It has thus been shown that in our hands the treatment of placenta previa becomes a matter of judgment, and the factors that will influence the choice of method are: situation of the placenta, amount of hemorrhage, the parous condition of the patient, whether labor has or has not commenced and how it is progressing, duration of the pregnancy, presentation of the child and whether it is alive and viable. Any of these factors may be influenced by a combination of the others. We believe that a selective choice of treatment in a sufficiently large series of cases will show results to justify it. All cases of placenta previa should be treated in the hospital, and many of the emergencies could be avoided

if the significance of first bleeding were appreciated. The selective treatment of placenta previa necessitates a careful vaginal examination. This should not be done until the patient is in the hospital, has been completely prepared, and the operating room set up to carry out any procedure found necessary.

Accidental Hemorrhage

Some years ago we came to the conclusion that the incidence of cesarean section on our service was too great. Twenty-five years ago our incidence of section was between 2 per cent and 3 per cent. This subsequently rose until in one year it was just under 5 per cent. Subsequent study led us to the belief that two conditions—heart disease in pregnancy, and accidental hemorrhage—were the principal factors giving rise to this unnecessarily high incidence. As a result of that study, our incidence of cesarean section has dropped from a high of 4.9 per cent of all deliveries in one year to 1.93 per cent during the last three years.

TABLE VIII. ACCIDENTAL HEMORRHAGE

TREATMENT	NUMBER	DEATHS
Conservative (including rupture of the membranes and forceps)	120	1 (anuria)
Bag	5	1 (sepsis)
Version	2	
Cesarean	11	
Classical	7	1 (cardiac failure)
Porro	4	
Undelivered	1	1
	139	4 (2.9%)

Table VIII is an analysis of the treatment of 139 cases of accidental hemorrhage. In this series only 11 were treated by section, seven of them by classical section and four by Porro section. There was a total mortality of four, or 2.9 per cent. Of these four deaths one was due to anuria following conservative treatment, one was due to sepsis following the introduction of a bag, one was due to cardiac failure ten days after classical section, and the fourth patient died undelivered. We believe that the principal place for cesarean section in the treatment of accidental hemorrhage lies among patients at the two extremes of the condition. In a few mild cases, where the baby is alive and labor has not started, section may save a baby that might otherwise be lost. At the other extreme are the severe cases of uterine apoplexy in which the uterine wall is infiltrated with blood to such an extent that it is unlikely that it will improve sufficiently to expel the fetus. Even in these latter cases we would not think it advisable to operate upon a patient suffering from severe shock until transfusion and other methods of treatment have succeeded in restoring her general condition. Occasionally we have found that in the severe cases, where our first treatment is that of shock, by the time the shock is overcome the patient has already started in labor and may then proceed to a spontaneous delivery.

Table IX gives the fetal mortality. In all cases of accidental hemorrhage it is 60 per cent in our series, and we do not believe that this figure would be

TABLE IX. STILLBIRTHS AND NEONATAL DEATHS IN ACCIDENTAL HEMORRHAGE

TREATMENT	NUMBER	DEATHS	PER CENT
Cesarean	11	9	81
Other methods	128	73	57
	139	82	60

TABLE X. CESAREAN SECTION FOR ANTEPARTUM HEMORRHAGE, 1928 TO 1944

	NUMBER	DEATHS
Total deliveries	16,115	
Total sections	312	
Sections for placenta previa		44
Sections for accidental hemorrhage		11

markedly reduced by routine cesarean section. Indeed, we do not believe that such a procedure would reduce our mortality below 3 per cent.

Table X is an analysis of all our cesarean sections done for antepartum hemorrhage.

Summary

1. There are presented the results of selective treatment of 191 cases of placenta previa with a mortality of 2.6 per cent, and 139 cases of accidental hemorrhage with a mortality of 2.9 per cent.

2. These results, we believe, are comparable to those obtained by routine section in the treatment of these conditions and may avoid the additional risk of subsequent pregnancies by patients who have undergone cesarean section.

3. All cases of antepartum hemorrhage should be treated in the hospital if at all possible, and as the diagnosis cannot always be accurately made when the first bleeding is only slight, this will entail hospitalizing patients who may subsequently be proved to have neither placenta previa nor accidental hemorrhage.

4. In most emergencies of medical practice, where special skill is not available, conservative measures of treatment are usually in the best interests of the patient, but in placenta previa and probably in accidental hemorrhage, if skilled judgment is not available, radical method of treatment, namely cesarean section, is probably advisable.

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Discussion

DR. BENJAMIN P. WATSON.—Dr. Scott's conclusions are very much those that most of us have arrived at regarding this subject, and I have already stated my views on it, viz., that there are really only two methods of treating placenta previa: (1) by doing nothing, or by simply rupturing the membranes, and (2) cesarean section. Which of those two methods one adopts depends, as Dr. Scott says, on all the circumstances surrounding the particular case. I know that there are clinics in this country where a patient who comes in with bleeding in the last trimester of pregnancy is immediately taken to the operating room and a cesarean section performed. With that method of treatment I cannot agree any more than Dr. Scott. Placenta previa is one of those conditions in which obstetric judgment is required and obstetric experience counts.

In cases of separation of the normally situated placenta there is a trend, especially pronounced in Boston, for the more conservative treatment of those cases. I think a great many

of the cases which are subjected to cesarean section could very well deliver without it and probably with no great increase in the fetal mortality. In the severe cases, where the patient has sudden severe pain accompanied by shock, with a ligneous uterus, it is extremely difficult not to do a section because the patient looks in extremis, even after the primary treatment of the shock. Prompt delivery seems to be called for. It is just a question, however, whether, even in those cases, we would not get an equally good result by rupture of the membranes. We know when we open the abdomen in such a case that the uterus looks purplish-black in color, is extremely tense, is not undergoing any sort of rhythmic contraction; and yet, when the uterus is opened and the tension inside is relieved and the placenta and baby are removed, it goes into contraction, so that one may safely sew it up and leave it. The same result may be attained, even in such cases, if we had the courage simply to rupture the membranes, thus relieving the extreme tension and restoring the circulation in the uterine wall, so that the uterus would take on regular contractions and expel the baby and placenta per vaginam.

We have all noted in those cases when a section is done, that there is very little bleeding from the uterine wall and there is very little fresh blood loss from the placental site. So I think we should be more inclined to treat cases of accidental hemorrhage by more conservative means, namely, rupturing the membranes and allowing the uterus to expel its contents normally.

DR. EDWARD G. WATERS.—I do not believe it possible to outline a plan for management of abruptio placentae by a group appraisal of statistics. The parity of the patient and condition of the cervix are most important deciding factors. A separation of cases into mild and severe is almost imperative. The basic threat is death from shock and hemorrhage. The mild cases will respond to any sensible therapy. In the severe form one must decide whether, after combating shock and blood loss, it is safer to empty the uterus quickly by cesarean section or temporize in the hope that the patient will deliver vaginally without the additional risk of an abdominal operation. In arriving at the decision, medically remote experiences in similar cases possess only comparative value as against those managed more recently with freely used blood transfusions, blood plasma, and other antishock therapy, and modern forms of anesthesia.

In our clinic [The Margaret Hague Maternity] we believe that cesarean section fills an important place in treating severe abruptions. During the six years prior to 1943, we found in 414 abruptions of all types, that cesarean section was used in 72 patients, mostly with the severer form. There were only two deaths in the entire group, and none in the cesarean group. In view of such experiences, we believe that abortion is a real indication for cesarean section in many of the severe forms, especially in patients with "unprepared" cervix.

I have used one practical procedure in our clinic which may be of value to those who have not tried it. In some of our cases, section disclosed a severe degree of myometrial disruption, the uterus failed to respond to oxytocics, and the patient's condition precluded a hysterectomy. When faced with this formidable state of affairs, a rapid ligation of the uterine arteries proved lifesaving. The vessels are quickly and easily exposed by extending laterally the transverse vesico-uterine peritoneal incision and mass chromic catgut ligatures are passed around the artery on each side.

The major circulation and blood loss are immediately checked with a minimum of operative trauma. The anoxemia induced in the uterine musculature institutes a prompt and prolonged muscular contraction. The flabby uterus contracts, hemorrhage stops, and the patient is saved further and possibly fatal operative work.

DR. ALFRED C. BECK.—On our service at the Long Island College Hospital we are in accord to a large extent with the conclusions of Dr. Seott.

I do not agree with Dr. Watson in regard to the patient who is in a critical condition from accidental hemorrhage. That is not the case for surgery; that is the type of case which

is best treated conservatively. That is the case that we began to treat conservatively thirty years ago and we have not regretted our stand in those cases.

We do cesarean section for accidental hemorrhage in the early cases when the child is alive, largely in the interests of the child, but in these critical cases in shock with the loss of a lot of blood we prefer to treat the shock, rupture the membranes, and give pituitary extract, and in most of those cases they deliver and survive.

DR. HOWARD C. TAYLOR, JR.—This series of cases has been presented as if an identical policy had been pursued for seventeen years. I would like to ask Dr. Scott if that is a correct assumption, or whether he can describe some of the changes in viewpoint which have taken place during that period of time.

The title of his paper is "The Selective Treatment of Bleeding During the Last Trimester of Pregnancy." In his tables he emphasized particularly the many varieties of treatment used, especially in placenta previa. Dr. Watson, however, has concluded that there are only two methods of treating placenta previa—leaving it alone or resorting to cesarean section. I want to ask Dr. Scott whether, during the course of these seventeen years, his treatment has not tended to be less selective and more standardized.

In regard to premature separation of the placenta, I would like to ask whether the results particularly as regards the baby were not different when the cesarean rate was very low as compared with the previous policy in which it was very high. The infant mortality in those two sets of statistics, based on contrasted over-all policy, is the figure, we would like to know. It does not help to be told that in 9 out of 11 cesarean sections babies died because, as you saw, those were the bad cases. What we need to know is the total infant mortality rate with sections in 20 per cent of the cases as compared with the infant mortality rate when the cesarean section rate is high.

DR. HARVEY B. MATTHEWS.—I can subscribe to Dr. Scott's conclusions by and large except that I would like to put in a good word for the bag. Dr. Watson and I always differ on that and while I have no statistics on hand on the use of the bag, I know we have used it frequently in certain types of placenta previa, namely, marginal or partial, and have obtained good results, without undue infection following its use, with good control of hemorrhage, and successful delivery of the baby. So that while I agree with Dr. Watson that the two main principles or common methods of treatment of placenta previa are rupture of the membranes and cesarean section, yet there are some cases in which the bag can be used successfully, and those of us who were trained at the old Sloane Hospital under Dr. Voorhees and Dr. Cragin know that we can use bags successfully in certain cases.

In conclusion, I would like to say that while I would not want to see the bag discarded altogether in the treatment of placenta previa, we must agree that the two main methods of treatment are: let it alone, and cesarean section.

DR. RALPH L. BARRETT.—I have been a member of the Special Committee on Maternal Welfare in New York County for the past several years. From my own clinical experience and from the studies of this committee, I agree with Dr. Watson and must disagree with Dr. Matthews on the use of the bag in the treatment of placenta previa. Personally, I would be pleased if all bags were discarded in the treatment of this condition. Our statistics show that the bag has been the method of treatment in many of the deaths from placenta previa. Suitable cases, in which simple rupture of the membranes was the method of treatment selected, have done very well. The cases which have had an early cesarean under proper hospital facilities, has shown the lowest maternal mortality rate.

I do not think there is any in-between method of treatment. Either do an early cesarean section or, if the case is a partial previa in a multiparous woman with a partially dilated cervix, simply rupture the membranes and await delivery.

Dr. Scott's paper shows that the majority of deaths in his series occurred in those cases where bag or versions of breech extraction was the method of treatment. It is this group of

cases that showed the highest mortality rate both for mother and baby. In general, his results as outlined in this paper were excellent, but I wish he would drop the bag and version in the treatment of placenta previa.

DR. SCOTT (closing).—I quite agree with Dr. Watson that in a case of accidental hemorrhage with a hard, distended, ligneous uterus the membranes should always be ruptured as soon as possible.

Dr. Taylor's question was much to the point. There has been a change in our practice in seventeen years, but probably not so much as he might think. I have pointed out that our incidence of section rose from about 2.5 per cent to 5 per cent and is again back to 1.9 per cent of all deliveries. There has been some slight change in our management of both types of antepartum hemorrhage. Such change is inevitable where judgment is the basis of procedure. Probably my judgment will be influenced to some extent by the discussion we have had tonight. In hospital practice, packing certainly should disappear, and version probably should do so. The latter may have a place in practice remote from hospitals. In the use of the bag there has been some change, and we certainly use it less frequently than we did fifteen years ago. We still think, however, that it has a place in properly selected cases, and I should hate to see it not available on our service.

Dr. Waters' remarks are worthy of consideration, and one would have liked a more detailed analysis of all these cases, but this was impossible in the time at my disposal. As I pointed out, the question of when to do a section in cases of severe abruptio placentae is a matter of judgment, and in a given case his judgment might be different from mine. Over the period under discussion we have become much more conservative, and with increasing experience we have courage to treat conservatively cases that previously would have had a section. There has not been a cesarean section for accidental hemorrhage during the past three years, and our mortality rate has not gone up.

A HISTOLOGIC STUDY OF THE EFFECT OF IRRADIATION ON ADENOCARCINOMA OF THE ENDOMETRIUM

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THE use of irradiation in the therapy of adenocarcinoma of the endometrium has attracted widespread attention. The early results of radium therapy in this disease were not encouraging, due perhaps to the fact that inadequate dosage and distribution were used. The recurrence of symptoms in the presence of active tumor after irradiation may occur only after long intervals so that hastily drawn conclusions as to the effectiveness of the irradiation are unjustified. Accordingly, long periods of time must elapse after therapy before results can be assessed and as yet very few reports satisfy this requirement. Numerous preliminary reports are available in the literature regarding the effectiveness of radium or radon alone. Especially notable are the reports from the Radiumhemmet in Stockholm. In this country more attention has been directed toward the combination of irradiation and surgery, in the hope of improving the cure rates obtainable by surgery alone. Another factor contributing to the increased use of radiotherapy has been the need for some form of at least palliative therapy in those patients who are unsuitable for the surgical attack either because of known extension of the tumor or because of the presence of some contraindication to surgery such as diabetes, heart disease, or obesity. Most of the evaluation of radium therapy has been on the basis of clinical results in terms of five- or ten-year cure rates, or in increase in survival rates, and little attention has been paid to the correlation of these results with histologic findings.

X-ray irradiation has also been used in the treatment of this disease. In some instances this has been used alone and in others in conjunction with radium irradiation. A third group has been treated by a combination of x-radiation and surgical therapy. Again study has been directed toward clinical cure and survival rates among patients subjected to these types of therapy, as compared with those treated by surgery alone. Reports dealing with the presence of viable carcinoma cells in operative specimens are extremely few.

Since it is likely that complete eradication of the tumor by whatever means of therapy is employed is essential to the production of cure, it seems logical to examine the effect of irradiation therapy on the carcinomatous tissue. The purpose of this paper is to present a series of fifty-three cases of adenocarcinoma of the body of the uterus, which were proved by examination of tissue obtained by curettage, and which have been treated either by a combination of radium application and surgery, or by radium, deep x-ray, and surgery. The material for histologic study was obtained by subjecting the patients to panhysterectomy with bilateral salpingo-oophorectomy at approximately five weeks after the completion of the irradiation therapy. The gross material has been carefully restudied and multiple blocks of tissue from each uterus were sectioned.

Few similar reports are found in the literature. Healy and Cutler,¹ reported on a series of patients treated by many combinations of irradiation therapy and surgery. They noted a few cases in which there was no demonstrable tumor in the uterus, but did not state how extensively the uterus was searched. The dosages of radium and x-ray employed, as well as the interval between this therapy and surgery, varied considerably. It was concluded that the well-differentiated tumor was most readily eradicated. Healy,² in a general report on irradiation therapy in malignant disease of the female generative tract, stated that (in adenocarcinoma of the endometrium) "very little viable carcinoma, and in more than half of the cases no carcinoma at all, could be found in the uterus on microscopic examination after its removal." The dosages employed are not stated, nor is there any statement as to the thoroughness of the search for the tumor. Operation was done in these cases four to six weeks after the completion of the irradiation. Arneson⁴ reported on ten cases treated by the insertion of two or more capsules of radium in tandem into the cavity of the uterus, followed by operation in from two to eight months. In four of the six cases which received more than 3,000 mg. hr. of radium irradiation, no carcinoma was demonstrable. Active tumor was found in every case which received a smaller dose. Again the extent of the search for tumor was not stated. E. Marquis⁵ reported persistent carcinoma in 21 of 29 uteri removed six weeks after being subjected to 55 to 60 mc. destroyed of radium (7,260 to 7,920 mg. hr.). He did not describe the method of application of the radium, nor did he indicate how extensive was the search for tumor in the excised specimens. Healy and Brown⁶ searched the uteri of 75 women with adenocarcinoma of the body of the uterus. These had been removed six to eight weeks following irradiation therapy. Of these, six which were treated with deep x-ray alone all showed residual carcinoma. The remaining 69 patients were all treated with radon, therapy having been given in each case by means of two or three capsules in tandem, each capsule being 15 mm. in length, and the combined capsules having a strength of from 75 to 150 millicuries. Three of 24 cases (12 per cent) treated with 1,200 to 1,700 mc. hr. showed complete regression of the tumor, 13 of 25 cases (52 per cent) given 3,000 to 3,300 mc. hr. showed complete regression, as did 12 of 20 cases (60 per cent) given 3,400 to 4,000 millicurie hours. They stated that "a careful microscopic examination" was done on these uteri. Corseaden⁷ in his discussion of this paper stated that only 8 of 21 patients treated by him showed no carcinoma on examination of the uterus after irradiation and operation, but he gave no details of therapy or of search.

In the course of his description of a hysterostat for intrauterine application of radium and of its use in eight patients, Friedman⁸ reported eradication of the tumor in seven. All of these patients received at least 4,000 mg. hr. of radium irradiation. He did not give any details as to the thoroughness of the search for residual tumor in these cases, in which the uteri were removed four to six weeks after irradiation therapy. Smith⁹ reported 24 cases of adenocarcinoma of the uterus treated with 2,400 to 3,600 mg. hr. of radium irradiation delivered from tandem capsules. A few of these patients also received 1,600 r. (point of measurement not given) by deep x-ray. When the uteri were removed four to seven weeks later, only four were completely free of tumor. The extent of the search was not stated.

The findings in a series of 46 patients treated with radon in single applicators on whom hysterectomy was carried out four to six weeks later were reported by Donovan and Warren.¹² The uteri of only five of these patients were free of carcinoma on routine examination of representative areas. The dosages employed in these cases varied widely. One patient received only 1,700 to 2,000 mc. hr., but her uterus failed to show residual carcinoma. Five of six receiving 2,000 to 2,500 mc. hr. showed tumor remaining, as did all of six receiving 2,500 to 3,000 mc. hr., 17 of 18 receiving 3,000 to 3,500, 11 of 13 receiving 3,500 to 4,000, and two receiving 4,000 to 4,500 millicurie hours. Schmitz, Sheehan, and Towne¹³ published in 1943 a report on 77 cases of adenocarcinoma of the corpus uteri. Among these were eleven in which the uterus was removed following irradiation. In five who received what they term "adequate" therapy, no carcinoma was found, while in the remaining six which received less than adequate therapy, grossly recognizable carcinoma was present in every instance. Four patients among seven others receiving adequate therapy underwent subsequent curettage. In none of these was carcinomatous tissue demonstrable. However, one of these patients died

of metastasis within a year. Carcinoma was found in three of six patients who had had inadequate therapy and subsequent curettage. These authors defined adequate therapy as 6,000 mg. hr. of radium irradiation given in three doses of 2,000 mg. hr. each at intervals of from seven to eight days, application being made in the Y-capsule described by Schmitz and Schmitz.³ This is followed by deep x-ray therapy. "The dose attained within the pelvis after twenty-eight days was 4,000 roentgens, with backscatter." Operation was done at intervals varying from three to eight months after irradiation in the five patients in whom no residual tumor was demonstrable. In these, the entire endometrium was blocked, and numerous sections were cut from each block, in the attempt to find tumor tissue. Of the remainder in which some type of surgical procedure was carried out in addition to the irradiation, the interval between these varied considerably.

Another report appearing in 1943, that of Scheffey, Thudium, and Farrell,¹⁴ included thirty cases of adenocarcinoma of the uterine fundus in which the combined therapy had been given. Fifteen of these thirty showed no tumor in the specimen removed eight to ten weeks after completion of irradiation. Of the nine patients who received 4,000 to 5,000 mg. hr. there were only two whose uteri contained demonstrable tumor. The method of radium application here was two or three 50 mg. capsules in tandem, left in position long enough to deliver the desired dose. No statement was made as to the thoroughness of the search for tumor in these specimens.

Examination of these results brings out a number of significant points. In the first place there is little agreement as to what constitutes adequate dosage in the irradiation therapy of adenocarcinoma of the corpus uteri. The variations are considerable, and perusal of other reports concerned with the treatment of this neoplasm by means of radium or radon supplies additional evidence of this. Success is not likely to be achieved where inadequate dosage has been employed. Better results have been obtained when at least 4,000 mg. hr. of radium irradiation or its equivalent in millicurie hours where radon has been used have been given. Wide variation is noted as well in the methods of application.

The majority of those quoted above^{4, 6, 9, 12, 14} used either single applicators or capsules in tandem, while Friedman⁸ used a hysterostat and Schmitz and co-workers¹³ used a Y-applicator. Irradiation may be expected to be ineffective if either distribution or dosage is uncontrolled. Heyman¹⁰ pointed to this fact in stating that the results at the Radiumhemmet had been improved when multiple capsules were packed into the cavity of the uterus instead of the single tandem applicator. Friedman⁸ showed by the use of an ingenious series of models that the ordinary methods of application fail to deliver adequate tumor dosage to all parts of the corpus. His hysterostat was designed to overcome this and to overcome as well the difficulties in delivering adequate dosage in those uteri whose cavities are distorted by the presence of other pathology such as myomas. Since the latter are frequently found in the presence of adenocarcinoma of the endometrium, and since these may on occasion markedly distort the uterine cavity, the control of distribution of dosage is essential.

X-ray therapy was used either alone or in conjunction with radium by the authors of four of these papers.^{1, 5, 8, 13} Here again there was little agreement as to dosage requirements. The measurement of the amount of irradiation energy delivered to the tumor area received attention in only one paper. Schmitz and co-workers¹³ reported a calculated depth dose. The others contented themselves with mentioning the use of x-ray or stating that a given number of roentgens were delivered without reference to the point at which the measurement was made. It may be concluded that the value of deep x-ray in the therapy of adenocarcinoma of the endometrium is not yet proved.

Author's Study

The present study is based upon 53 patients with adenocarcinoma of the body of the uterus who were treated for this condition at the University of

Minnesota Hospitals during the years 1939 to 1943, inclusive. All had both irradiation therapy and surgery. With one exception all the patients studied had their complete therapy in this institution. One patient received 3,600 mg. hr. of radium irradiation elsewhere. This was delivered from three capsules in tandem. She was transferred here to receive 219 per cent ESD (2,190 tissue roentgens) measured at the uterus over twenty-eight days and for subsequent total hysterectomy. All patients received radium irradiation prior to surgery. In seven this was given from two or three capsules arranged in tandem in a single long applicator, while in the remaining cases the radium was arranged in a jointed tandem applicator to be described below. Twenty-three patients had deep x-ray therapy prior to operation as well. Twelve of these received more than 250 per cent ESD to the uterus as above (100 per cent ESD equalling 1,000 tissue roentgens), over about four weeks, and eleven received a lesser amount. This was discontinued as a routine procedure on July 1, 1941, and since then only preoperative radium irradiation has been used.

In the instances where the straight tandem was employed, the amounts of therapy were as follows: two cases, 2,000 mg. hr. of radium irradiation; one case, 2,400 mg. hr.; one case, 2,500 mg. hr.; one case, 3,600 mg. hr. plus 219 per cent ESD of deep x-ray therapy; one case, 4,000 mg. hr. plus 200 per cent ESD; and one case, 4,900 mg. hr. plus 155 per cent ESD. Table I gives the amounts of therapy in those patients treated with the jointed tandem applicator. Those patients who received it were given deep x-ray therapy first, usually over the course of about four weeks, and this was immediately followed by radium application. When the full dose of radium irradiation had been received, the patient was discharged from the hospital, to be readmitted about four weeks later for operation, total hysterectomy and bilateral salpingo-oophorectomy being carried out. In one case there was a three-year interval between the completion of the irradiation and operation. It had been planned originally to treat this patient with irradiation alone, since she was quite obese and had diabetes and chronic cholecystitis, but the appearance of vaginal bleeding prompted eventual hysterectomy. In another patient the interval was three months, as the patient had hyperthyroidism, necessitating subtotal thyroidectomy. In all other instances operation followed the completion of irradiation therapy by 4 to 8 weeks.

TABLE I. THERAPY IN 46 PATIENTS TREATED WITH JOINTED TANDEM APPLICATOR

RADIUM (MG. HR.) GIVEN OVER 100 HR.	DEEP X-RAY (IN ESD TO UTERUS OVER 4 WEEKS)			TOTALS
	NONE	250% OR MORE	LESS THAN 250%	
4,500 or more	23	10	7	40
Less than 4,500	3	2	1	6
Totals	26	12	8	46

In forty-six cases a jointed tandem applicator was used. This was designed to overcome the objections to straight tandem applicators and to permit of easy application. The uterine cavity is directly measured. Five capsules with platinum walls 1 mm. in thickness contain the radium element and are placed in series in a long piece of rubber tubing, the capsules being fixed in position by firmly ligating the tubing between adjacent capsules. The resulting triangle has two capsules on each side and one at the base, and must accurately fit the uterine cavity. The applicator will bend to some degree to accommodate itself to varying shapes of the cavity. As well, the length of each capsule within the tandem can be varied to suit the depth of the cavity and the width of the fundus. For smaller uteri a three-capsule triangle is used. In the usual five-capsule setup, 45 to 50 milligrams of radium are applied over the course of 100 hours to deliver 4,500 to 5,000 mg. hr. of radium irradiation. The practice has

been to place in succession in the tubing capsules containing 7, 10, 15, 10, and 8 mg. of radium, respectively. The combined effects of these when formed into a triangle will produce a diffuse dose to the cavity. In applying the radium, the rubber tube is bent double between the second and third capsules and in this shape is slipped into the cavity. Preliminary dilatation of the cervix is carried out if necessary. When the fundus is reached the shorter arm of the applicator is held stationary while the longer arm is introduced more deeply. This has the effect of causing the middle capsule to come to lie transversely across the fundus. In most instances the introduction of this applicator is a rapid and simple matter.

The uteri were removed at an arbitrary four to five weeks after the completion of the irradiation, and immediately after operation routine sections were made of any suspicious areas. When there was no gross evidence of carcinoma, sections were taken from two or three areas in the fundus and cervix. These have been reviewed, and those uteri which were apparently free of carcinoma at the time of the original examination have been re-examined. In order to make sure that no carcinoma was overlooked, the entire endometrium, together with the musculature underlying it to a depth of 0.7 to 1.0 cm., was removed, and sections were made at intervals of not more than 3 mm. at right angles to the surface. It was felt that there was very little chance of carcinoma escaping detection by this method.

TABLE II. RESIDUAL CARCINOMA

AMOUNT OF X-RAY	4,500 OR MORE MG. HR. RADIUM IRRADIATION			LESS THAN 4,500 MG. HR. RADIUM IRRADIATION		
	NO.	CARCINOMA PRESENT	%	NO.	CARCINOMA PRESENT	%
None	23	13	56.5	3	2	66.7
250% ESD or more	10	4	40.0	2	1	50.0
Less than 250% ESD	7	3	42.8	1	1	100.0
Totals	40	20	50.0	6	4	66.7

In 27 of the total of 53 uteri (50.9 per cent) residual carcinoma was found. Carcinoma which was deep in the muscular wall but showed none at the surface of the endometrial cavity was found in 19. Of these 19, 17 were discovered on routine section, while the remaining two were found during the course of the present study with complete sectioning of the endometrial cavity surfaces. In these two there was no surface carcinoma, but extensive tumor growth was seen in the myometrium. Three of the uteri showed carcinoma both at the surface and in the muscle, while in five, surface tumor was present without invasion of the muscle being evident.

In the seven patients treated with a single straight tandem applicator, there were three instances of residual carcinoma. The incidence was 42.8 per cent. Two of the cases received only 2,000 mg. hr. of radium irradiation, while the third received 4,900 mg. hr., together with 155 per cent ESD of x-radiation at depth. In all these cases the tumor was discovered on routine examination.

Forty-six of the uteri had been treated by other means than the straight tandem radium applicator. Of these, 24 were found to have apparently viable residual carcinoma, and in 22 it was discovered on routine examination of the operative specimen. Forty of the 46 patients received at least 4,500 mg. hr. of radium irradiation, the great majority receiving at least 4,900 milligram hours. Residual carcinoma was found in 20, or 50 per cent. X-ray therapy was not given to 23 of these patients, and in 13 of this group, an incidence of 56.5 per cent, residual tumor was present. Seven of the remaining 17 who received deep x-ray therapy as well as radium irradiation showed residual carcinoma in the excised uteri, with an incidence of 41.2 per cent. The six remaining patients in the series received less than 4,500 mg. hr., and of these four had residual carcinoma. These results are summarized in Table II.

The microscopic appearances of the sections taken from the uteri of these patients showed wide individual variations. Three rather distinct pictures were seen in the uteri where there was no viable carcinoma, and any combination of the three could be seen in a given instance, although usually one picture predominated. A few of the uteri showed complete necrosis of the

endometrial surface, and not infrequently this change extended into the musculature. For a depth of several millimeters the tissue was converted into a homogeneous pink-staining mass. Cell boundaries were entirely lost, and a few fragments of material staining intensely with hematoxylin were all that remained of the nuclei. Usually a zone of small round cells, polymorphonuclear leucocytes, and hemorrhage, with some formation of granulation tissue, marked the boundary between the necrotic area and the surviving muscle. The irregularity of the boundary zone in some places suggested the possibility that infarction, as well as cell death as a direct result of the radium, may have played a part in the production of the marked necrosis.

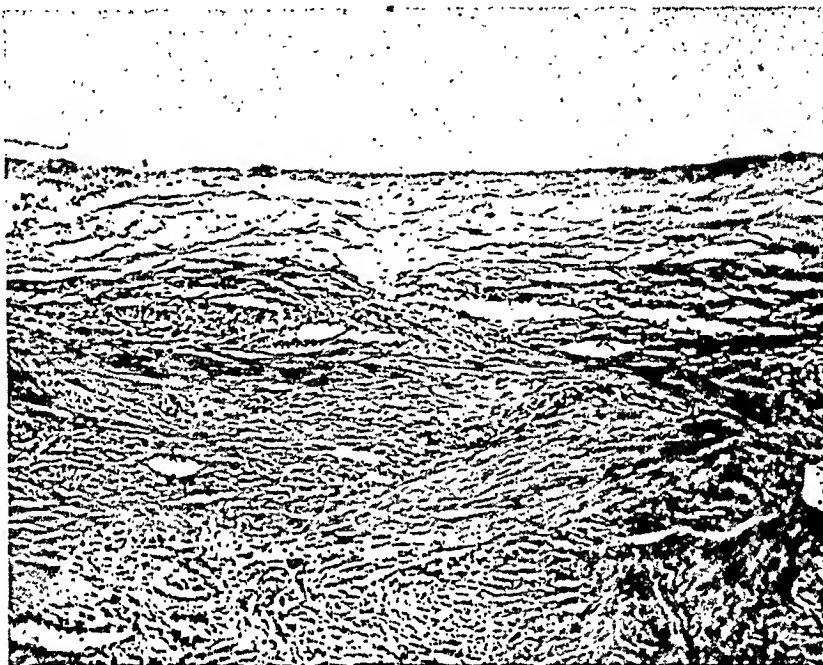


Fig. 1.—(X100). Endometrial surface of uterus after irradiation, showing complete eradication of tumor tissue. See description in text.

In the majority of instances where residual tumor could not be demonstrated, the microscopic appearance was that of Fig. 1. The lining of the endometrial cavity has been changed to a zone of rather loose granulation tissue in which are seen a few small blood vessels. At the surface the tissue is denser, and occasional swollen, finely granular surface epithelial cells are seen. Immediately beneath the zone of granulation the myometrium begins. It appears relatively unaffected, is perhaps slightly atrophic, and there are only scattered small round cells. This section was taken from the uterus of a 51-year-old white woman which was removed four and one-half weeks after the completion of 4,900 mg. hr. of radium irradiation, given because of a proved adenocarcinoma of the endometrium.

Fig. 2 illustrates a section taken from the uterus of a 46-year-old white woman four and one-half weeks after completion of 4,900 mg. hr. of radium irradiation, and is typical of the next most frequent microscopic picture. Here again there is a zone of loose granulation tissue quite similar to that in Fig. 1. In addition, however, a number of irregular gland spaces are seen. These are lined by distorted epithelial cells whose cytoplasm is granular, more than usually eosinophilic, and slightly vacuolated. Nuclei are moderately pyknotic. It is not possible to say whether these are endometrial glands or represent damaged carcinoma, but it is felt that the former is more likely from the general pattern. Scattered small round cells are also seen.

In those instances where viable tumor was present the pattern was entirely characteristic of adenocarcinoma. Fig. 3 shows one such area. This section was taken from the uterus of a 53-year-old woman removed six weeks after the completion of 4,900 mg. hr. of radium irradiation.



Fig. 2.—($\times 100$). Lining of endometrial cavity after irradiation showing cleftlike glandular spaces lined by columnar epithelium. For description, see text.

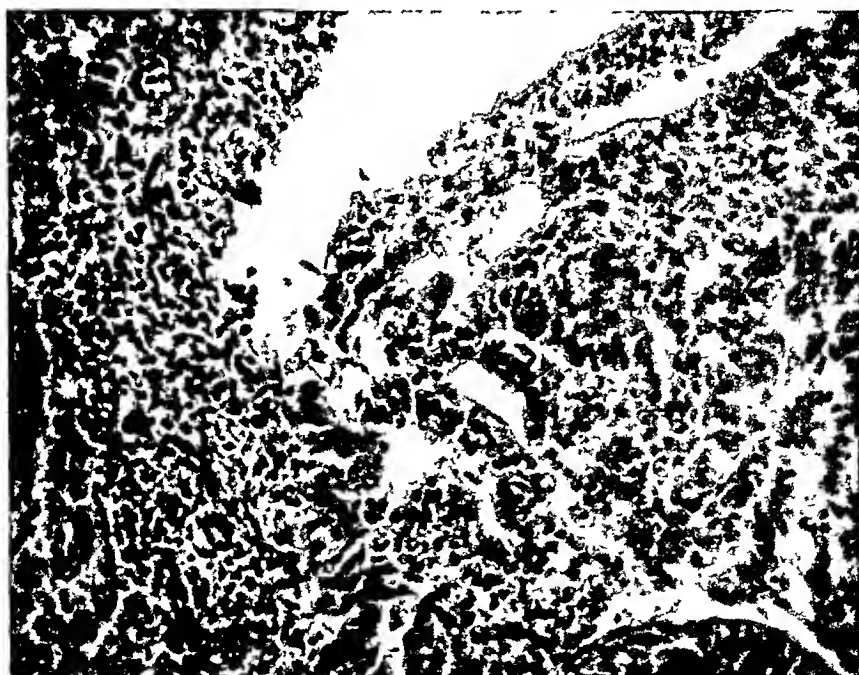


Fig. 3.—($\times 270$). Lining of endometrial cavity after irradiation showing relatively little effect on tumor tissue. See text for description.

tion. Viable tumor at the endometrial surface, and as well the base and stalk of a polypoid growth of tumor, are seen. There is some evidence of irradiation effect upon the tumor cells, but it is not marked. Round cells are grouped beneath the tumor, but are probably the natural concomitant of the latter rather than evidence of irradiation effect. Other areas in this section showed greater damage to the tumor, amounting to complete destruction on occasion, but they were distributed very irregularly. This general picture was typical of the instances where surface tumor remained. Undamaged tumor was always present to some degree, frequently in close apposition to areas of advanced degeneration. It must be pointed out, however, that some areas of complete necrosis or destruction of the surface tumor were always seen, and this is in contrast to the picture when only tumor in the depth of the muscle remained. In Fig. 4, a portion of a section taken from the uterus of a 74-year-old woman, removed about five weeks after 125 per cent ESD of deep x-ray irradiation and 4,500 mg. hr. of radium irradiation had been given, tumor tissue is seen deep in the muscular wall of the uterus. There is little evidence of irradiation effect on the tumor cells. A few are slightly swollen and granular, but the majority are undamaged.

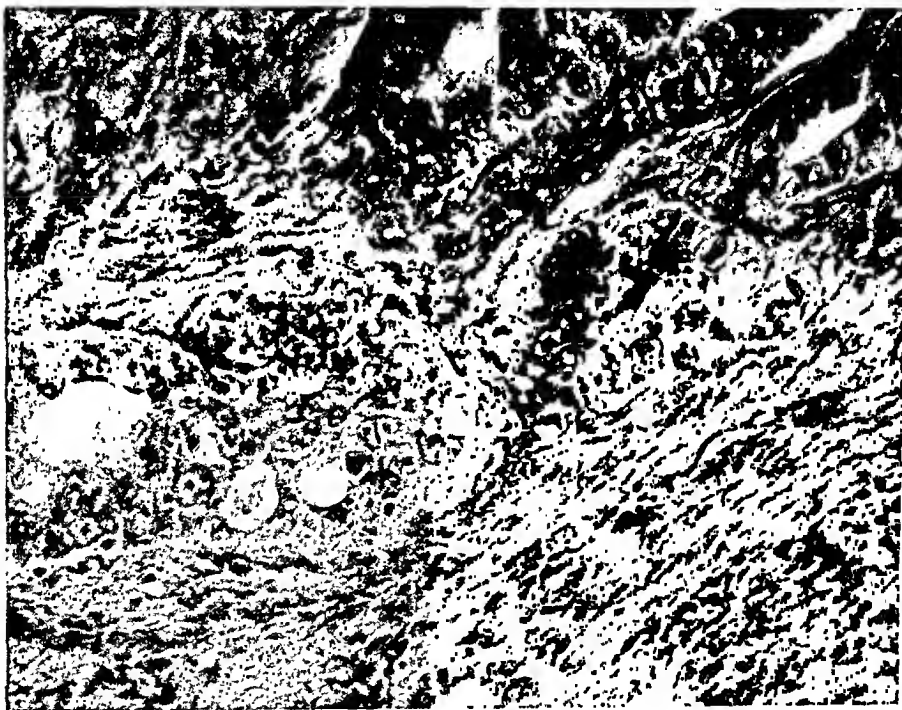


Fig. 4.—(X270). Section of uterine wall taken postirradiation. Viable tumor seen in the muscle. Description in text.

Discussion

It is apparent that eradication of adenocarcinoma of the body of the uterus is not attainable by these methods of irradiation therapy. The fact that residual carcinoma was found to be present in the uteri of a high percentage of these patients, even in the most heavily treated group, makes it quite clear that surgery must continue to have a place in the attack on this disease. This concept is borne out by the reports quoted earlier which showed that residual carcinoma was absent only occasionally after irradiation. In the great majority of the reported studies there was a fairly high incidence of carcinoma present following various forms of irradiation therapy.

Several factors must be taken into account in assessing the value of irradiation treatment of any type in eliminating carcinoma. In the first place one must of course consider the possibility that the entire growth may have been removed at the time of curettage. This might conceivably occur when the tumor is revealed quite early in its course before invasion of the uterine musculature has taken place, the tumor being limited to a small area on the endometrial surface. One might suspect this situation when not all of the material obtained at curettage is carcinomatous.

Second, the total amount of therapy must be considered. One cannot expect complete elimination of the neoplasm where inadequate amounts have been employed in spite of the fact that in occasional instances cure will apparently be produced by small amounts. It has already been emphasized that the distribution of radiation energy must be such as to deliver the maximum dosage possible to the tumor, and it felt that the applicator described in this paper has been successful in effecting this in this small series. The uteri of 12 of the 46 patients thus treated showed distortion of the outline of the endometrial cavity because of myomas or adenomyosis uteri interna. Exactly half of them contained residual tumor, and in every instance it was found deep in the musculature, no tumor being seen at the surface. Among the uteri the outline of whose cavity was unchanged the incidence of residual carcinoma was slightly over 50 per cent, and in seven of these, surface carcinoma was present. The persistence of viable tumor deep in the muscle might be a consequence of inadequate irradiation of the tissues at even small distances from the source of energy. Arneson and Hauptman¹¹ have pointed this out in connection with the use of straight tandem applicators, and have shown greater effect on both surface and deep tumor when the distribution of energy is improved.

Other factors are more likely to account for this persistence of tumor in the depth of the muscle after irradiation. Tumor is seen to persist in the musculature even when it is close to the endometrial surface. No scarred areas have been found in the musculature after irradiation as one might expect if tumor had been present and been destroyed. In other words, no evidence has been obtained from this study to suggest that tumor which has invaded the muscle to lie beneath the surface is ever destroyed by irradiation. On the other hand, it has been clearly demonstrated that tumor in the musculature of the uterus often does escape destruction in spite of maximum irradiation. The clinical significance of this is obvious.

Finally, the role of deep x-ray therapy must be considered. The short series reported here seems to indicate that the combination of adequate amounts of radium irradiation plus adequate amounts of deep x-ray therapy should produce results, as far as the elimination of tumor tissue is concerned, which might be expected to better those produced after the use of radium alone. It must be emphasized, however, that the number of patients so treated is not great enough to enable one to assert that the addition of x-ray to the plan of therapy is necessarily worth while. The application of the Chi-square formula indicates that the difference noted in this series is not statistically significant. An increase in the frequency of complications following the use of x-ray therapy seem to be

out of proportion to the advantages obtained. This will be reported in detail elsewhere. Undoubtedly the problem deserves much further study before an authoritative answer can be given.

Summary and Conclusions

1. The literature dealing with the detection of residual tumor and its frequency in adenocarcinoma of the endometrium treated with radium, radon, and deep x-ray therapy has been reviewed. These reports show persistence of apparently viable tumor in from 12.5 per cent to 89 per cent. There was wide variation in the amount of therapy given, in the type of radium or radon applicators used, in the intervals between irradiation therapy and operation, and in the thoroughness of the search for residual tumor in the operative specimens.

2. The incidence of residual tumor in the uteri of the 53 patients studied in this paper was 50.9 per cent. All of these patients had intrauterine radium application; 23 had deep x-ray therapy as well. In a small series where x-ray was employed in adequate dosage together with radium irradiation, the incidence of residual tumor fell to 40 per cent, while in a longer series where radium alone was used the incidence was 56.5 per cent.

3. An applicator designed to overcome the effect of variations in size and shape of the uterine cavity is described. It was used in forty-six of the fifty-three cases.

4. In the majority of instances where residual carcinoma was found, it was seen in the musculature of the uterus. The significance of this is discussed.

5. In view of the fact that tumor persisted after irradiation in a high percentage of cases, and especially in view of its frequency in the myometrium, it is concluded that surgical attack must be considered to be the essential feature of curative therapy in the treatment of adenocarcinoma of the corpus uteri. It is still possible that preliminary irradiation may be useful as additional therapy or as palliation.

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THE MANAGEMENT AND TREATMENT OF THE LATE TOXEMIAS OF PREGNANCY*

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BY "toxemia of pregnancy" is understood a disturbance occurring during or in connection with pregnancy, consisting of a variety of syndromes, the most constant factors of which are hypertension, proteinuria, and edema. To these may be added a variety of renal, gastrointestinal and nervous symptoms, the most important of the last being convulsions and coma. The disease is most protean in its clinical manifestations. Yet there is no general agreement as to whether there is, in the words of Goodall, "one toxemia of pregnancy," the multiform manifestations depending on one as yet undetermined specific cause, as typhoid fever and syphilis in all their varying clinical pictures depend on their respective specific causative organisms; or whether, as Dieckmann and many others believe, a number of different causes may operate in the pregnant woman, to give rise to a more or less similar group of manifestations.

In an attempt to standardize present concepts of pathologic and symptomatic variations into an admittedly imperfect but at least widely acceptable and workable system of nomenclature, the American Committee on Maternal Welfare adopted the now familiar system of nomenclature which is currently in more or less general use.

Group A. Disease not peculiar to pregnancy:

- I. Hypertensive disease (hypertensive cardiovascular disease)
 - a. Benign (essential), mild, severe
 - b. Malignant
- II. Renal disease
 - a. Chronic vascular nephritis or nephrosclerosis
 - b. Glomerulonephritis
 - (1) Acute
 - (2) Chronic
 - c. Nephrosis
 - (1) Acute
 - (2) Chronic
 - d. Other forms of severe renal disease

Group B. Disease dependent on or peculiar to pregnancy:

- I. Pre-eclampsia
 - a. Mild
 - b. Severe
- II. Eclampsia
 - a. Convulsive
 - b. Nonconvulsive (that is, coma with findings at necropsy typical of eclampsia)

Group C. Vomiting of pregnancy

Group D. Unclassified toxemias

*Presented by Dr. Cosgrove before The Hamilton Academy of Medicine, Hamilton, Ontario, Dec. 5, 1944, and The Toronto Academy of Medicine, Toronto, Ontario, March 6, 1945.

Pre-eclampsia.—Mild: "Mild pre-eclampsia" is the term applied to that condition which may arise during pregnancy, almost always after the twenty-fourth week, characterized by a moderate rise in systolic blood pressure to about 140 to 160, and a diastolic blood pressure of 90 to 100 mm. Hg. The urine contains less than 0.6 Gm. of albumin per 100 c.c. and the edema is usually slight and rarely may be absent; usually no changes are demonstrable in the retinal arteries.

Severe: A condition, which usually becomes evident after the twenty-fourth week of pregnancy, is characterized by a sustained systolic blood pressure of more than 160 and usually a diastolic blood pressure more than 110 mm. Hg, usually accompanied by the passage of more than 0.6 Gm. of albumin per 100 c.c. of urine. The edema is severe in most cases. Usually hypertensive changes may be observed in the retinal arteries.

As already stated, this system of nomenclature is not completely satisfactory, as its proponents very clearly recognize, but it is capable of use as a serviceable medium of thought exchange. The destructive criticism of it contributes nothing to the useful potentialities of helpful interchange of experience. Such interchange of experience, however, is necessary for progress in our understanding and handling of the disease. This nomenclature by its wide adoption provides a medium of such commerce which, granting any of its imperfections, is capable of being just as useful as is the far from puristic "pidgin English" of the Orient, in material barter and exchange.

The pathology of the disease is as various as its symptomatology. Any of the important viscera may partake more or less extensively of the pathologic changes. Among the more constant pathologies are those involving the liver, the kidneys, the brain, the vascular system, the heart, the adrenals, the pituitary, and the organs of special sense, notably the eyes. Yet there is no absolutely pathognomonic picture. There is no single lesion which will permit the pathologist, without reference to the clinical history of the case, to say on the one hand, "This woman certainly *had* eclampsia," or on the other hand, "This woman certainly *did not have* eclampsia."

Ideas of pathogenesis are of course closely linked with shifting conceptions of pathology. At the very dawn of the modern era of physiologic chemistry, the constant and frequently severe degree of proteinuria led observers to consider toxemia as primarily a form of nephritis, or uremia. The variation in severity of the renal lesions, however, even in clinically most severe and fatal cases, forced the abandonment of this idea. About the turn of the century, attention was critically focused on the frequent and significant changes in the liver. At that time observers *did* believe that the hepatic changes were of one pattern that was pathognomonic of the disease. Extreme variations in the type and severity of liver pathology, however, eventually in turn forced abandonment of belief in an absolutely pathognomonic pattern in this organ, while at the same time important pathologies of other organs obtruded their significance. Most recently there has been a recognition of definite functional and structural changes in the vascular system, particularly the capillaries and arterioles. This seems to be the common denominator present in all observed visceral pathologies, and of their hemorrhagic components. This has led to the acceptance, by many astute observers, of these changes in the blood-vascular system as the most significant and universal pathologic tendency.

The search for an ultimate pathogenic basis of the disease, apart from its broad association with pregnancy itself, has been assiduous and painstaking for nearly a century. The term, "toxemia," of course connotes some specific poison or toxin circulating in the blood, comparable to bacterial toxins of certain specific diseases, which are responsible for the clinical manifestations of those diseases. Hence, physiologic chemists and bacteriologists alike have arduously sought the existence and identity of such an agent, completely without success, so that up to the present time the very term toxemia cannot be logically justified. The association of the disease with the presence within the maternal organism of a living conceptus has of course concentrated the search for such a pathogenic factor to a very large extent on the products of fetal and placental metabolism. Besides, all the other fields of physiologic disturbance, such as the endocrinopathies, dietary and nutritional variations, the allergic states, have been fine combed in vain.

Therefore, in regard to the pathogenesis of eclampsia, we even today might properly paraphrase the immortal Omar to the effect that,

"Myself when not-so-young did eagerly peruse,
Doctor and doctor and heard great argument,
About it and about, but evermore came out
By the same door wherein I went."

Because in 1883, Barnes said, "There has been going on a most active inquiry as to the etiology of puerperal convulsions, with . . . frequent modification of theory; but, even at the present day science has not settled the question." Many years later, Whitridge Williams said, "It is apparent that the cause of eclampsia has not yet been discovered." To neither of these statements am I able today to add one single word.

Lacking then a guide in the form of any established knowledge of etiology and pathogenicity, the management and treatment of the late toxemias of pregnancy remain on exactly the same basis upon which our fathers established it. It presents three phases: (1) prophylaxis; (2) the treatment of symptoms; (3) the termination of the pregnancy. The only changes that the years have seen have been some improvement in the average level of medical awareness of the diagnosis and treatment potentialities of the earlier stages. By this I mean that the leading writers of two generations ago expressed a knowledge of the principles of treatment which would be, at least broadly, entirely acceptable today. It is very certain, however, that this knowledge was not at that time so thoroughly and usefully disseminated among the rank and file of the profession as is the thought of the leading authorities of today. Hence, far fewer victims of the disease derived the benefit of principles which had already been well established.

All of this is interestingly shown in a comparative table (Table I).

The present practice of our Clinic will be briefly summarized. Details will of course vary with the individual case, and to some extent with the three service chiefs, equal in clinical authority, who are responsible for the work.

TABLE I

IN 1880

IN 1944

I. Prophylaxis Stressed

It consists of frequent contact with the patient; the regulation of her general hygiene and diet; watching her for morbid manifestations

(1) in general symptoms, especially weight gain and edema

(2) in urinary anomalies

By chemical and microscopic findings

(3) in blood pressure variations

By sphygmograph, available to but few observers

(4) in blood chemistry abnormalities

By few and crude methods

Plus a variety of renal function tests

By the better sphygmomanometer, universally available

By many easily available methods, but with no greatly significant results

II. Symptomatic

A. In the presence of indications of toxemia

(1) Rest in bed

(2) Fresh air

(3) Dietetic

Restriction of dietary proteins best exemplified in exclusive milk diet

Restriction of salt, compensation for protein loss, rarely by water restriction

(4) Stimulation of gastrointestinal elimination by salines

By a great variety of active mineral and vegetable purgatives

By enemas—occasionally by castor oil and high colonic irrigations. Lavage

(5) Stimulation of kidneys by copious liquid intake; by digitalis

By saline diuretics; by dry or wet cups; by leeches

By intravenous administration of hypertonic glucose; occasionally hot fomentations; high colonic irrigations; occasionally synthetic diuretics

(6) Reduction of hypertension by venesection

Esteemed of utmost importance.

Rarely used. Believed generally transitory only in effect

(7) Induction of labor

B. Convulsions having actually supervened

(1) Isolation, quiet, good nursing, protection from injury

(2) Purging

Elaterium or croton oil, or calomel or jalap

Not so universally used, but still stressed by some, especially the Dublin School

(3) Venesection

Most important measure

Used occasionally by most authorities

(4) Control of convulsions

By chloroform—augmented by morphine and chloral; *Veratrum viride*

By morphine—augmented by chloral and chloroform by Stroganoff; chloroform condemned by most Americans. By magnesium sulfate intravenously. By various synthetic drugs, especially the barbiturates. Veratrone

(5) Termination of pregnancy

Up to recent years regarded as paramount by most authorities, but even in early days some advocated conservatism. In the early years of this century accouchement forcé much used and much abused. Barker said (1883): "Whenever delivery by art can be effected by less irritation than would be produced by the continuance of the child in the parturient canal, it should be resorted to." This statement, I believe, is still eminently valid.

The pendulum of opinion in recent years is strongly conservative. The greatest teachers of our day almost accuse one with the temerity to advocate radicalism of murder. Their statistics are frequently unfair, however, in contrasting brutal accouchement forcé without selection of cases, with their conservative treatment, rather than making the comparison with modern operative techniques and innocuous methods of anesthesia. They give little consideration to fetal survival

Method of Treatment

Prophylactic treatment includes the entire regime of antenatal care. This connotes frequent close observation of all pregnant women from the earliest time possible. History, blood pressure, urinalysis, weight, general signs and symptoms should all be noted and carefully analyzed from time to time.

If abnormalities indicative of toxemia develop, the regime must be intensified by rest, varying from minimal restriction of activity to hospitalization and complete bed rest. The last is the *most important single item* of prophylaxis and of the treatment of the milder cases. Diet must be restricted as to carbohydrates and total calories sufficiently to control excessive weight gain. In the presence of marked rapid weight gain, which usually indicates occult edema, or in any evidence of actual edema, salt should be restricted.

Simple urinalysis is supplemented by estimations of the renal capacity, of blood chemistry, and sometimes of hepatic function. The liquid intake and urinary output should be closely watched and correlated. Bowel function is maintained by mild catharsis, usually with salines, enemas, and, much less frequently than formerly, by high colonic irrigations. Only mild and minimal sedation is employed in cases of this mild type.

Failure of the mild type to improve under such a regime, or its progression to constantly more menacing symptomatology, should in a reasonably short time lead to the consideration of the termination of pregnancy. The means adopted will depend on age, parity, previous pregnancy and labor history, duration of pregnancy, viability of child, social, religious, and personal considerations peculiar to the individual patient, the severity of the condition, the presence of special symptoms, and the estimated imminence of disaster.

Means employed for this purpose are usually medicinal, comprising castor oil, enemas, and the exhibition of fractional doses of pitocin, sometimes augmented by artificial stripping and rupture of the membranes. Other mechanical means, such as bagging or the use of bougies, are rarely resorted to. It is generally preferable to make, if necessary, several attempts at such medical induction, rather than to risk not always promptly successful mechanical procedures with their high potentiality of infective complication. In the presence of fulminant progress of the case toward explosive eventuality, cesarean section for delivery should be unhesitatingly resorted to.

In this connection, the anesthesia is of great importance. No inhalation anesthetic should be used, but lower neuron anesthesia by local infiltration, intrathecal or caudal instillation, should be employed.

In those types of late pregnancy toxemia depending on pre-existing disease, as the nephritides, and the various forms of fixed hypertension, the same general regime is applicable except that the medical management must be more rigorously instituted and maintained and more prompt resort to termination of the pregnancy must be carried out. The importance of this time factor will be discussed in greater detail presently.

If the patient develops or is first seen in an actual state of eclampsia, the following outline of treatment is carried out:

1. Segregation of the patient, darkening of the room, elimination of all possible causes of disturbance from the environment, provision of competent, constant nursing care.
2. Provision of facilities to guard the patient against injury during convulsions.
3. The administration of 20 c.c. of a 10 per cent solution of magnesium sulfate intravenously at one-hour intervals as long as convulsions persist. As their frequency subsides, the dosage is progressively cut down to four-, eight-, and twelve-hour intervals. It is continued at the last rate for at least twenty-four hours after convulsions have stopped.
4. An initial dose of morphine sulfate $\frac{1}{4}$ grain by hypodermic may be given. It is usually not repeated because of its respiratory depression.
5. Other sedatives such as bromides, chloral, various barbiturates may be used. If they are, they should be used in substitution for, rather than in addition to, morphine and magnesium sulfate. Every sedative available in eclampsia is itself a poison. To multiply the number of such agents simultaneously given to one patient is to risk the incalculable synergistic effect of several poisons on a woman already manifestly severely poisoned. Determine what sedative you will rely on, then stick to it!

6. Three hundred cubic centimeters of 25 per cent dextrose solution are given intravenously and repeated at intervals of from four to twelve hours. This acts to reduce edema and as a direct diuretic. The rate of administration of this solution should not exceed 4 c.c. per minute.

7. Draining of tracheal mucus by inverted posture of the patient and by direct aspiration is practiced when necessary.

8. Venesection is used only in right heart failure.

9. Liquids of high carbohydrates equivalent are given as soon as the patient has recovered consciousness and can swallow.

10. It will be noted that this scheme of management does not contemplate any effort to terminate the pregnancy, during the actual period of convulsion and/or coma. Labor may occur spontaneously during this phase of the patient's condition and progress to successful termination. Even when this occurs, however, no artificial interference is employed, except occasionally very simple low forceps extraction to expedite the delivery. We have not for many years resorted to cesarean section in the presence of actual eclampsia, inasmuch as we believe, on the basis of long-time experience, that this increases the hazard to the mother and that the prospect of fetal salvage is very, very small.

However, if the patient recovers from the eclamptic crisis undelivered and with a viable baby, we believe that within a period of a very few days the pregnancy should be terminated as already described under prophylaxis. We feel that she has reverted to a status of severe pre-eclampsia and may be in very definite danger of recurrence of eclamptic seizure.

Results

The Margaret Hague Maternity Hospital has now been in operation a little over thirteen years, during which time there have been born approximately 70,000 living babies. This material has embraced many hundreds of toxemia patients. For several years Dr. Leon C. Chesley, our biochemist, has been very much interested in all phases of this subject. Together with a number of co-workers, notably his wife, Betty Chesley, and Drs. Willard Somers and John McGeary of our staff, both now in the Army service, he has been especially interested in follow-up of this group. From these follow-up studies certain valuable points of emphasis in relation to the management already outlined may be deduced.

The primary objective of all management is (1) to reduce maternal mortality. The most direct secondary objectives contributing to this primary purpose are (2) the prevention of eclamptic convulsions, and (3) the prevention of abruption of the placenta. Next to the life hazard of the mother, (4) the life hazard to the fetus in abortion, stillbirth, and neonatal death becomes the most important consideration of management. Finally (5) the reduction of remote hazard of death to the mother by the prevention of permanent sequelae, notably fixed hypertensive states, is a further objective.

A summary of 1,625 cases of toxemia occurring in a five-year period, 1935 through 1939, shows:

A maternal mortality of 1 per cent.

An incidence of abruption of the placenta of 3.8 per cent.

An incidence of eclampsia of 5.5 per cent.

An incidence of total fetal loss of 17.1 per cent.

An incidence of remote permanent hypertension of 53 per cent.

The whole question of treatment, therefore, depends on how much we can reduce these several hazards, the protection against which are the objectives of treatment.

In this connection it must be immediately recognized that prophylaxis cannot, except possibly in a very small degree, prevent the actual occurrence of toxemia. The most that prophylaxis can accomplish is recognition of the very first danger signals of toxemia in order that further management may avert in some measure the hazards under consideration.

Our statistics would appear to show that the prompt control of even the mildest cases of toxemia is essential in cutting down those hazards, because they increase definitely with the progress of the disease from milder to more severe forms. Thus, we had only one death in 1,232 cases of mild pre-eclampsia, renal disease, and unclassified toxemia, but there was one death in every twenty-four cases of severe pre-eclampsia, eclampsia, and hypertensive disease. The appearance of convulsions increased the maternal mortality rate almost ten times.

But it is further noteworthy that not all cases exhibit systematic progression in severity. One cannot assume that a case of *mild* pre-eclampsia is in no danger of eclampsia because she has not progressed to a *severe* grade of pre-eclampsia before the onset of convulsions. Almost two-thirds of all our eclampsia occurred in cases which we had considered mild pre-eclampsia. Or, to state the equation the other way around, one out of every 29 of our mild pre-eclampsias became abruptly eclamptic without exhibiting any intermediate phase which would warrant their consideration as severe pre-eclamptics.

Much the same consideration holds for the incidence of abruption of the placenta. While it is true that the incidence of this condition did increase with the severity of the toxemia, it still occurred in mild pre-eclamptics in a ratio of 1 in 50 cases.

Thus, from the standpoint of the mother, in order to protect her from the possibility of abruption, of eclampsia, of a high mortality rate, and the later occurrence of fixed hypertension, the prompt control of an existing toxemia of any grade whatever would appear to be paramount. The only effective means accomplishing this control is termination of the pregnancy. Therefore, the crucial consideration is the time interval between the first exhibition of any degree of toxemia whatever, and the termination of the pregnancy.

How does such prompt termination affect the interest of the baby? This, of course, would depend somewhat on the period of gestation. Before thirty-four weeks the baby is more or less surely jeopardized by prematurity. Hence there would appear superficially to be an a priori conflict of interest between the mother and the baby. This conflict is more apparent than real, however. While it is true that the baby, prior to this period of gestation, is more seriously jeopardized by prematurity, the continuance of its intrauterine existence by no means insures a better life prognosis. Many of these infants die in utero, apparently of the direct effects of the mother's illness on the fetus. Should the mother develop either abruption or eclampsia, these conditions per se represent a tremendous hazard to fetal survival. If these three fetal hazards be offset against the single fetal hazard of prematurity, it is apparent that the fetus is not much more significantly jeopardized by the termination of the pregnancy at any time from the period of viability up to the thirty-fourth week than it would be if the pregnancy were carried further in the assumed interest of the fetus.

After the thirty-fourth week, the termination of the pregnancy in the mother's interest would appear to act just as significantly in the fetal interest, because the baby from this time on is subjected to much less of a hazard by reason of prematurity, while the longer the pregnancy continues, the greater becomes the hazard to the fetus of the other three factors discussed above.

Thus it can very definitely be stated that prompt termination of the pregnancy in the presence of established toxemia after the thirty-fourth week of gestation serves alike and directly both the maternal and the fetal interest.

It also serves to prevent fixed hypertension as a sequela of the toxemia. This clinical condition, or rather symptom, is selected as a gauge typifying all the sequelae of pregnancy toxemia because of its ease of estimation and the relative frequency with which it occurs as compared with other possible sequelae. Also, it is important as indicative of the progressive vascular-renal disease probably constituting the aftermath of such toxemias.

Survey of the actual medicinal components of the management of toxemias in our clinic shows a wide variety of specific agents and combinations of such agents, from which no sure conclusion can be drawn as to the outstanding comparative value of any. It is probable that this statement might be extended to apply just as validly to all the many agents, combinations of agents, and so-called methods or systems, which have been everywhere employed.

What have been the results of the vast amount of work which has been performed in the attempt to reduce toxemic mortality in pregnant woman? In a broad statistical sense there has been a real and fairly regularly progressive reduction in such mortality. But it is noteworthy that this decrease in maternal hazard from toxemia has been closely parallel to the general decrease in maternal mortality from all causes. This is to some extent natural and understandable. The improvements in general prenatal observation, in surgical technique, in nursing technique, in knowledge and resources having to do with the replacement of lost blood volume, and in chemotherapy, which have contributed so tellingly to the reduction of hazard in the other great causes of maternal mortality, namely, hemorrhage and infection, have all benefited equally the toxemic patient. Beyond the influence of such factors common to all the causes of maternal death, we believe that the improvement already obtained in deaths from toxemia, and the promise of greater improvement depend upon:

1. The general employment of close prenatal supervision of all pregnant women.
2. Recognition of the actual appearance of toxemia at the earliest possible time.
3. Increasing hospitalization of pregnant women.
4. Prompt institution of bed rest and suitable medical treatment of even mildest cases.
5. The early interruption of pregnancy in all cases, except those of the mildest type whose symptoms entirely clear up under rest and medical regime. This is especially important beyond the thirty-fourth week of gestation.
6. The elimination of meddling midwifery of all sorts from the management of the convulsive toxemias.

ORAL THERAPY WITH ETHINYL ESTRADIOL IN THE MENOPAUSE

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THE value of estrogenic preparations in the treatment of the menopausal syndrome is firmly established. Ever since chemically pure estrogens became available, the medical profession has sought earnestly for compounds which, when given orally, have the distinction of high potency, good tolerability, and economy. In 1938, Inhoffen and Hohlweg³ prepared a derivative of estradiol by replacing the hydrogen atom at carbon atom 17 with an ethinyl group. It is claimed that the new compound fulfills the requirements of great effectiveness when administered by mouth, of comparative absence of unpleasant side reactions, and of inexpensiveness. Clinical results with ethinyl estradiol in climacteric patients have been described only by a limited number of investigators; hence a report of further experiences along these lines seems warranted.

Material and Procedure

The series under investigation consisted of 53 patients, ranging in age from 34 to 51 years, who were suffering from climacteric symptoms. There were 27 cases of natural menopause, 21 cases of surgical menopause, and 5 cases of radiologic menopause. In 15 patients, bleeding which still persisted ranged from oligomenorrhea to hyperpolymenorrhea. Almost all patients complained of hot flushes, diaphoresis, tingling in extremities, and other symptoms which may be classified as vasomotor nervous or general. As for basal metabolic dysfunction, two-thirds of the patients stated that there was a weight increase of fifteen pounds or more during the last few years. A history was taken in every case and the patient thoroughly examined—this included a careful pelvic examination. In all those exhibiting excessive bleeding, the presence of intrauterine pathologic processes was ruled out by means of a diagnostic curettage.

The cytology of the vaginal epithelium was studied in all cases. Smears were taken before treatment, and several times during and after. The single differential stain was used according to the simplified technique of Shorr.^{6*}

In addition, pre- and postmedication biopsy studies were performed in ten cases in order to determine the effect of ethinyl estradiol on the endometrium.

Finally, in seven of these patients and in three others of the series, assays of urinary prolans and estrogens were performed prior to initiation of therapy.

The prolans were assayed in a morning specimen and the estrogens in a twenty-four-hour specimen. The prolans were extracted by utilizing the modification of Zondek's method. A fresh refrigerated specimen of urine was slightly acidified with dilute acetic acid. Ethyl alcohol was added and the mixture allowed to stand from two to twenty-four hours, then centrifuged and the supernatant fluid discarded. Ethyl ether was added, well shaken in order to break up the precipitate, which removes the estrogenic substances, again centrifuged and the supernatant fluid discarded. The precipitate was dried until all ether had evaporated. Distilled water was added and constantly shaken for ten minutes, again centrifuged and the

*The Kit devised by Dr. Brent of Roche-Organon, Inc., which contains all the material necessary for the preparation of vaginal spreads, proved most practical for this purpose.

supernatant fluid, which contains the gonadotrophic hormone, saved. Three immature female mice weighing from 6 to 8 grams were injected twice daily for three days. The mice were not injected on the fourth day and were autopsied on the fifth day or one hundred hours after the first injection.

The estrogens were extracted by using the Kurzrok and Ratner method. Nine hundred cubic centimeters of the twenty-four-hour urine specimen were made slightly acid with dilute acetic acid, then saturated with sodium chloride. The treated urine was then covered with ethyl acetate to the top of the flask. A second flask was filled with 200 c.c. of ethyl acetate and attached to the first flask. The hot plate was turned on to medium heat and the ethyl acetate distilled over, and condensed. It dropped to the bottom of the first flask from which it returned to the second flask. The drops of ethyl acetate in passing upward through the urine extracted the hormone. This provided continuous extraction for forty-eight hours. The extracted urine was then discarded and the ethyl acetate extract, which contains the hormone, was concentrated by vacuum distillation. To the remaining substance 6 c.c. of propylene glycol were added. This solution was then injected into ovariectomized rats. The animal assay consists of injecting a definite dosage of the solution in three equal doses, and twenty-four hours later making a vaginal smear. A positive smear must show the cornified cells characteristic of estrus.

No hormone estimations were carried out following termination of therapy, partly because of the expense involved, and partly because the patients, no matter how cooperative they were while symptoms were severe, did not want to "bother" with collecting the urine specimens once they had found relief.

At the initiation of the investigation, one tablet containing 0.05 mg. of ethinyl estradiol* was given three times a day. If side effects occurred, the medication was stopped for four days and the dosage then reduced to 0.05 mg. a day, and this was increased later as needed. This plan was found unsatisfactory and was abandoned. Instead each patient was started on 0.05 mg. a day, given in two divided doses, and this whenever indicated was increased after a few days to a daily total of 0.1 mg. and sometimes to a daily total of 0.15 mg. In general, before shifting to maintenance dosage, the maximum therapeutic dose employed in a given patient was kept up for three to four weeks. Then the daily dose was reduced; in many cases as little as 0.025 mg. (half a tablet) maintained the patient in comfort.

Clinical Results and Laboratory Findings

Satisfactory relief of symptoms followed administration of ethinyl estradiol in all cases within six to nine days. Forty-three women showed complete relief and ten were markedly benefited. Patients who were started on the original dosage plan (0.05 mg. three times daily) in general experienced relief sooner than those who were started on a daily dose of 0.05 mg. and whose hormonal intake was then built up gradually.

Significant side reactions occurred only in patients who from the beginning were given a total daily dose of 0.15 mg. Of these, 6 patients developed gastric distress after two or three days of medication. These undesirable by-effects subsided, however, on discontinuation of the drug and were not provoked again in any case on reduced dosage. In twelve patients, each of whom had received a total dosage of 3.15 mg., given over twenty-one days, withdrawal bleeding occurred when the dosage was reduced. Moreover, in eight cases there was withdrawal bleeding after cessation of medication. As for the total requirements, those patients who still continued to menstruate, although climacteric symptoms had begun, needed the smallest total dosage. In those women who had undergone natural menopause, a somewhat larger total dosage was necessary, and in cases of artificial menopause, the needs were still a little higher. However, in all of these groups the requirements were minute as compared with other oral estrogens.

Preliminary vaginal smears in the majority of instances revealed marked estrogen deficiency characterized by "atrophy" cells and an abundance of leucocytes. Smears studied

*The ethinyl estradiol tablets, (Lynoral) 0.05 mg., used in this study were supplied through the courtesy of Dr. Leo A. Pirk of Roche-Organon, Inc., Nutley, New Jersey.

when patients were changed to the maintenance dose usually showed good cornification. However, not in all cases did the smear picture parallel the subjective response experienced by the patient.

The premedication biopsy studies revealed an atrophic endometrium in five instances and some degree of proliferation in five others. Specimens, taken between fourteen and twenty days after initiation of therapy, showed a cystic and glandular hyperplasia of the endometrium in one instance, and good proliferation in all others.

Preliminary urinary prolans were present and estrogenic hormones absent in the cases investigated.

Case Reports

Four cases are reviewed briefly partly because their histories illustrate the procedure employed and the results obtained, partly because of the interesting features encountered.

CASE 1.—B. H., aged 50 years, para iii, gravida iii. Menarche occurred at 13 years of age with cycles of 28 days and a menstrual flow lasting three to four days. A year ago menstruation ceased abruptly. Patient complained of 24 to 28 flushes a day. Pelvic examination revealed: a normal vagina; a clean, multiparous cervix; a small, atrophic, movable uterus; and normal uterosacral ligaments and adnexae. The vaginal smear showed atrophy cells and leucocytes. A biopsy specimen revealed an atrophic endometrium. Urinary prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol were administered three times a day. After eight days there were only two to three flushes a day. The vaginal smear on the fourteenth day of therapy showed some atrophy cells and numerous well-cornified epithelial cells. An endometrial biopsy study carried out on the same day revealed good proliferation. The daily dosage of 0.15 mg. of ethinyl estradiol was well tolerated and maintained for three weeks. During this period there were only occasional hot flushes at night and consequently the dosage was shifted to 0.05 mg. a day. On this maintenance dose, which was kept up for three months, the patient did very well.

CASE 2.—H. W., aged 34 years, para i, gravida i. Menarche occurred at 15 years of age with cycles of 32 days and a menstrual flow lasting four to five days. In July, 1944, a panhysterectomy and bilateral oophorectomy had been performed. Three months postoperatively, patient experienced severe vasomotor symptoms which constituted her main complaint at the first consultation. The vaginal smear showed atrophy cells and leucocytes. In the urine, prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol were given three times a day. On the third day the patient developed gastrointestinal symptoms (nausea and vomiting) and consequently the medication was discontinued for four days. Thereafter on reduced dosage—0.05 mg. a day for three days—there was no recurrence of side reactions. Increase of dosage to 0.05 mg. twice a day was also tolerated well. This was kept up for eleven more days. At that time there were mild symptoms only, and a vaginal smear study on the seventeenth day of medication showed atrophy cells and small epithelial cells with large nuclei. Then the dosage was shifted to 0.05 mg. a day. On this maintenance dose, which was kept up for three months, the patient did very well.

CASE 3.—L. S., aged 48 years, para iv, gravida iv. The menstrual history was a normal one until three months prior to her presentation. At that time a severe menorrhagia required roentgen-ray castration. Patient complained of frequent hot flushes, marked vertigo, and nervousness. Pelvic examination revealed: a slight cystocele and rectocele; a clean, multiparous cervix; an antiflexed, movable uterus of normal size; and normal uterosacral ligaments and adnexae. The vaginal smear showed atrophy cells and small epithelial cells with large nuclei. A biopsy specimen revealed a proliferative endometrium. (Fig. 1A.) Urinary prolans were present and estrogenic hormones absent. Five-hundredths of a milligram of ethinyl estradiol three times a day was tolerated well and was followed by marked improvement.



Fig. 1A.—Case L. S., aged 48 years, radiologic menopause; preliminary endometrial biopsy showing a proliferative phase.



Fig. 1B.—Same case, after seventeen days of treatment with the higher dose of 0.15 mg. ethinyl estrodiol a day, showing cystic and glandular hyperplasia.

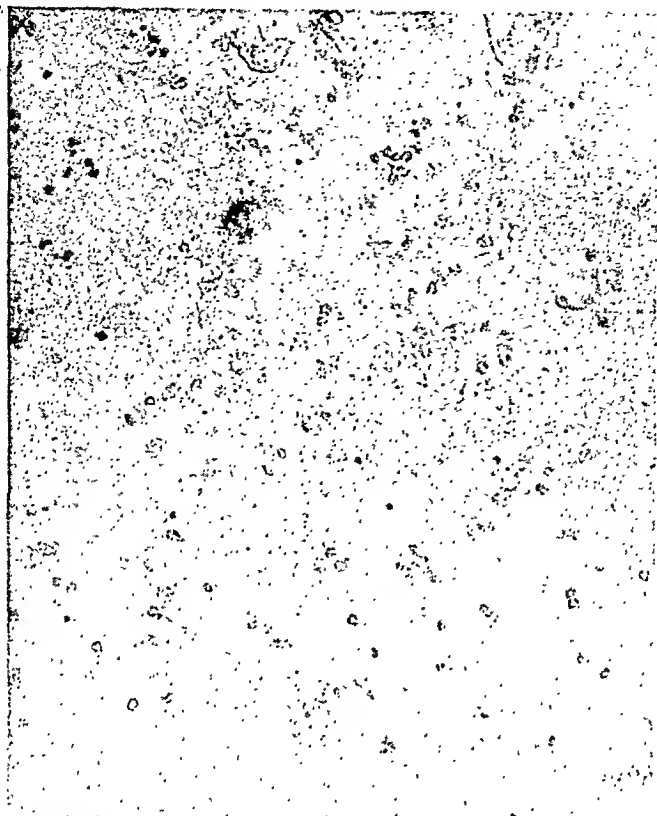


Fig. 2A.—Case M. W., aged 50 years, natural menopause; preliminary vaginal smear showing marked estrogen deficiency.

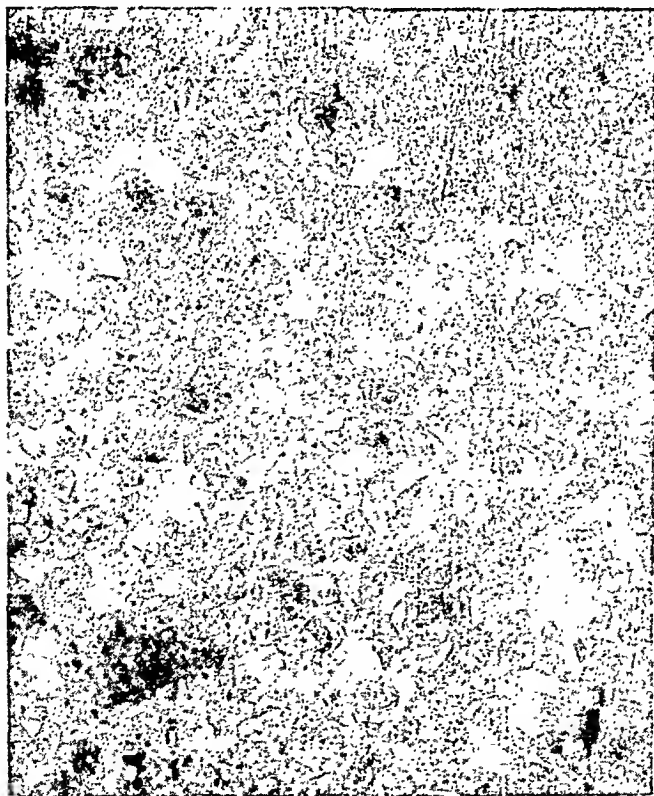


Fig. 2B.—Same case, after eighteen days of treatment with ethinyl estradiol, showing clean appearance and large epithelial cells with small pyknotic nuclei.

There were only one to two flushes after seven days of treatment. A vaginal smear, made after seventeen days under this regimen, showed complete cornification. An endometrial biopsy study carried out on the same day revealed cystic and glandular hyperplasia (Fig. 1B). Then the dosage of ethinyl estradiol was reduced to 0.05 mg. daily. On this maintenance dose, which was kept up for three months, patient was completely free of symptoms.

CASE 8.—M. W., aged 50 years, para ii, gravida ii. Menarche at 16 years of age with cycles of 28 to 30 days and a menstrual flow lasting three to four days. Menses had ceased one and one-half years ago. Patient had 20 to 30 flushes a day and with spells of vertigo for which she sought medical attention. Pelvic examination revealed: a normal vagina; a multiparous cervix with a slight erosion on upper lip; an anteflexed, movable uterus of normal size; and normal uterosacral ligaments and adnexae. The vaginal smear showed marked estrogen deficiency (Fig. 2A). A biopsy specimen revealed a proliferative endometrium. Urinary prolans were present and estrogenic hormones absent. Satisfactory clinical relief of symptoms was noted after one week, on a daily dosage of 0.1 mg. of ethinyl estradiol given in two divided doses. Thereafter patient was satisfactorily maintained on a daily dose of 0.05 mg. A vaginal smear taken on the eighteenth day of treatment was characterized by its clean appearance and large epithelial cells with small pyknotic nuclei (Fig. 2B). An endometrial biopsy study carried out at this time revealed late proliferation. A daily dose of 0.05 mg. of ethinyl estradiol was maintained for another three months and this kept patient completely free of symptoms.

Discussion

Table I summarizes some of the observations of other investigators who have discussed the use of ethinyl estradiol tablets in the menopause.

TABLE I. ETHINYL ESTRADIOL TABLETS IN THE MANAGEMENT OF THE MENOPAUSE AS REPORTED IN THE LITERATURE

REPORT	NO. OF CASES	FAILURE OF RESPONSE	DAILY DOSAGE FOR MOST PATIENTS
U. J. Salmon, S. H. Geist, R. I. Walter, and N. Mintz ⁵	22	2	0.45 mg.
B. A. Watson ⁸	18	1	0.45 mg., 3 days 0.30 mg., 2 days 0.15 mg., daily
M. J. Groper and G. R. Biskind ¹	33	4	0.05-0.45 mg.
S. D. Soule ⁷	30	2	0.05 mg.
R. A. Lyon ⁴	45	0	0.05 mg.
F. E. Harding ²	32	0	0.05-0.1 mg.

The series studied by the various workers consisted of from 18 to 45 patients. Relief was obtained in these groups in from 87.8 per cent to 100 per cent. This includes excellent as well as partial relief of symptoms. The daily therapeutic dosage ranged from 0.05 mg. to 0.45 mg. The incidence of toxic manifestations varied greatly in the hands of these investigators. Salmon et al.⁵ observed nausea, vomiting, abdominal pain and malaise, necessitating cessation of therapy, in four out of 22 patients. These side reactions were induced with 0.3 mg. of ethinyl estradiol as the daily dose. Three other patients had similar gastrointestinal symptoms which, however, subsided on reduced dosage. Of the 18 cases studied by Watson,⁸ only one patient experienced such severe side effects—nausea and urticaria—that the medication had to be discontinued. Even as little as 0.05 mg. a day elicited these symptoms. Another woman complained of slight nausea and soreness of the breasts and vagina. Groper and Biskind¹ in their series of 33 patients observed three instances of severe headache but in only one did it become necessary to discontinue the drug. Soule,⁷ who treated 30 women, found a daily dosage of 0.05 mg. to be therapeutically satisfactory. Under this plan he observed two instances of gastrointestinal symptoms requiring cessation of medication. Lyon,⁴ studying 45 patients, likewise employed a daily dosage of 0.05 mg. This induced slight nausea in five cases.

Finally, Harding² observed four instances of "true toxic reactions" (nausea, vomiting, dizziness) in his group of 32 climacteric women. These side effects were experienced on a daily dosage of 0.1 or 0.2 mg.; with smaller dosage in three of these cases toxic symptoms subsided. No attempt was made to reduce the dosage of the fourth patient.

In the present study undesirable by-effects—gastrointestinal distress—were observed only on a total daily dosage of 0.15 mg. in six cases. Symptoms disappeared promptly when the dosage was reduced to its minimal effective level. This was 0.05 mg. a day and there was no recurrence of symptoms in those patients whose daily dosage plan was later increased. But it is felt that in general and if symptoms are not too severe, satisfactory response is obtained with a daily dose of 0.05 mg. This is in keeping with the findings of other investigators, particularly those of Soule⁷ and Lyon.⁴ The fact that such a small dose of ethinyl estradiol is effective shows its high potency when given by mouth as compared with other estrogens which lose about 90 per cent of their activity when passing through the gastrointestinal tract.

Summary and Conclusions

A series of 53 women with menopausal symptoms was treated with ethinyl estradiol. All were satisfactorily relieved six to nine days after institution of therapy. The initial treatment plan, which called for 0.05 mg. of ethinyl estradiol three times daily, was abandoned since side effects occurred in 6 patients. By reducing the daily dose to 0.05 mg., gastrointestinal disturbance could be eliminated completely. Consequently, the initial daily dose in all patients was changed to 0.05 mg. This dose was tolerated well without exception and could be increased with impunity. The optimal therapeutic amount was given for three to four weeks after which the daily dose was reduced to a maintenance level.

Repeated vaginal smear studies were carried out in all cases. Endometrial specimens of ten patients were studied before institution of therapy and after ethinyl estradiol had been administered for two to three weeks. Premedication hormone assays were performed in ten cases.

Clinical results of other investigators with ethinyl estradiol in climacteric patients are discussed.

The new estrogen is very effective when administered by mouth. There is complete absence of side reactions if minimal effective doses are administered.

We wish to thank Dr. H. C. Taylor, Jr., for his constant advice and encouragement.

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PYRIDOXINE FAILURE IN NAUSEA AND VOMITING OF PREGNANCY

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HYPEREMESIS gravidarum occurs very infrequently. The less serious nausea and vomiting is far more common, but its incidence is difficult to evaluate because the patients may not report it, or they may not report for prenatal care until they have more or less passed the period of this distress. Nausea alone is thought to be frequent, and it is still more difficult to evaluate inasmuch as there is no physical or external means of proving its intensity, duration, and frequency. Dieckmann's⁷ definitions and classification are employed throughout. The purpose of this report is to present observations on the value of B₆ or pyridoxine as a therapeutic agent for nausea and vomiting of pregnancy.

Numerous chemical agents and procedures have been tried and used with varying degrees of success. Frequently a proponent will follow a given procedure for a given time and then finally discontinue its use without retracting his previously published recommendations. Thus, the literature remains flooded with endorsements which in many instances should have long since been retracted. Vitamins and vitamin therapy have been given credit for many values as therapeutic agents. There is no question about the place and need of certain vitamins in certain conditions.

Hart, Sydenstricker, and Torpin,¹ in 1941, used a pill which contained thiamine, riboflavin, nicotinamide, pyridoxine, and calcium pantothenate in the treatment of nausea and vomiting of pregnancy. They report that usually there was cessation of vomiting and partial relief of nausea within two to three days after treatment had been instituted. Furthermore, it was their conviction that, if this preparation had been instituted early in pregnancy and continued with one tablet after each meal, the patient would remain free from this annoyance of pregnancy. Recurrence would take place in one or two weeks, in some instances, after they discontinued the tablet. It should be stated that their series consisted of sixteen mild cases.

In 1942, Willis, Winn, Morris, Newsom, and Massey² used thiamine chloride and pyridoxine. Of 46 patients on thiamine chloride, good results occurred in 30; fair, in 10; and poor, in 6. Whereas, of the 37 patients on pyridoxine, good results were found in 25; fair, in 8; and poor, in 4. All their treatments were given intramuscularly and intravenously. In their article they state that "almost complete relief from nausea and vomiting of pregnancy was gained by administering vitamin B₁ and B₆ in varying dosage at irregular intervals and by either the intramuscular or intravenous routes." In spite of the fact that the percentages of good results are about comparable for thiamine and pyridoxine, they add that relief occurred from nausea and vomiting more often from the use of B₆ than B₁.

Weinstein, Mitchell, and Sustental,³ and Weinstein, Wohl, Mitchell, and Sustental⁴ have offered the following observations. The former group stated, "While the use of pyridoxine hydrochloride has proved of value in these 32 patients, the importance of sedation and adequate dietary supervision should not be overlooked, but should be prescribed as usual with pyridoxine hydrochloride used as an integral and valuable portion of this regimen." A few

months later, the latter group had increased their series from 32 to 78 patients. Relief was noted in 68 by the use of 30 to 80 mg. pyridoxine orally for the less severe patients and 100 mg. daily for the severe ones. Again they find that "the use of pyridoxine hydrochloride has proved of value in this group of 78 patients. However, the value of sedation and adequate dietary supervision should continue to command our attention, and should be utilized with pyridoxine hydrochloride as an important adjunct in the therapy of nausea and vomiting of pregnancy. A far larger series of patients must be carefully analyzed before final conclusions can be reached."

By contrast, Smith,⁵ making a report, did not give the data on the number of patients treated. He did recommend a complete history and physical examination, careful investigation for pyelitis, cystitis, abscessed teeth, and vaginal and cervical infection. He gave liver extract intramuscularly and 100 mg. thiamine chloride and 50 mg. pyridoxine hydrochloride intravenously daily for three days and then weekly as needed. The patients returned for further treatment only when the first signs of nausea reappeared.

Silbernagel and Burt⁶ had complete relief in 38 out of 40 patients by the use of intravenous pyridoxine hydrochloride. Their dosage varied from 25 to 50 mg. Twenty-two of this number had been on intravenous therapy with complete and permanent correction. Repeated injections were given only when symptoms recurred. They took special care not to alter the diet or to prescribe sedatives.

It is impressive that the above authors could collect in short periods the number of patients with sufficient symptoms to require treatment. At the Chicago Lying-in Hospital there are very few admissions with vomiting of pregnancy, and not all of these are classed as hyperemesis gravidarum. Only 2 of the 16 patients of our series required hospitalization and but 1 was a hyperemesis gravidarum case. Hence, the other 14 patients had only minimal or moderate nausea and vomiting. It is our contention that patients with hyperemesis gravidarum should be hospitalized to obtain proper treatment. The treatments for this series were given in two orders. The first group was placed on pyridoxine, 100 mg. daily by mouth and 100 mg. pyridoxine intramuscularly twice weekly. Out of the 11 patients that had pyridoxine initially, only 3 had good results, 3 had fair results, and 5 had poor results. Placebo therapy was used in 3, secondarily. One of these obtained good results on placebo therapy subsequently and another one had an excellent result with moderate sedation.

The control group consisted of 5 patients who were initially placed on placebo therapy. The tablets were the same size as the pyridoxine one and given in the same manner and number. Thus, when a change was made, the patient was not aware of it. Three of these 5 patients were completely relieved of their nausea and vomiting by sterile water intramuscularly injected and placebo tablets. Two had poor results and were later placed on pyridoxine. The one patient with hyperemesis gravidarum in the entire series was benefited only when electrolytes, body fluids, and other deficiencies were corrected in accordance with Dieckmann's⁷ routine.

Tables I and II give additional data about these patients, including age, the number of previous pregnancies and complications, and the weeks of gestation when treatment was instituted.

TABLE I. EFFECT OF PYRIDOXINE (B₆) UPON HYPEREMESIS, AND NEED FOR OTHER THERAPIES

CASE	AGE (YR.)	GRAV.	PARA	COMPLICATIONS		WEEKS PREG.	SUBSEQUENT THERAPY		REMARKS	RE- SULTS OF B ₆
				PRIOR PREG.	PRESENT		PLACEBO	OTHER		
1	22	i	0		Fear	12			Phenobar- bital for sleep	Good
2	26	ii	i	Stillbirth		10				Good
3	28	iii	ii	Stillbirth		8			"Doesn't need shots"	Good
4	22	ii	i	Endometritis		10		X		Fair
5	29	ii	i			8	X			Fair
6	30	ii	i	Breast ab- scess		9		X		Fair
7	26	i	0		Obsession	8		X		Poor
8	31	i	0			14	X (good result)			Poor
9	37	iii	ii			10		X (good result)		Poor
10	38	ii	i	Long labor; Dührssen incision		8		X		Poor
11	38	iii	ii		Twins	8	X	X		Poor

TABLE II. EFFECT OF PLACEBO THERAPY UPON HYPEREMESIS, AND NEED FOR OTHER THERAPY

CASE	AGE (YR.)	GRAV.	PARA	COMPLICATIONS		PREG. WEEKS	SUBSEQUENT THERAPY		REMARKS	RE- SULTS OF PLACEBO
				PRIOR PREG.	PRESENT		B ₆	OTHER		
12	23	ii	i			9				Good
13	27	ii	i	Abortion		8			Hospitalized	Good
14	35	iii	ii			6				Good
15	31	iv	ii	1 abortion 3 hyperemesis		7	X	X (good result)	Hospitalized	Poor
16	33	iii	0	Ectopic and abortion		8	X		"Hypos" helped most	Poor

Particular efforts were made to have the patients make no change in dietary and other habits and routines. All of those who failed to respond to either the pyridoxine or "placebo" therapy were cured by appropriate sedation and dietary management.

The less severe cases were treated for two or more weeks before changing the treatment if a good result had not occurred. The more severe cases and those hospitalized required relief in shorter time. Those in the hospital had 100 mg. pyridoxine hypodermically daily. This assured that the vitamin was not lost by vomiting or was not assimilated due to deranged gastrointestinal state. Possibly two weeks was too short a minimum time, but those carried longer appeared not to do any better.

When good results, or arrest of vomiting and relief of nausea took place, it did so usually within a few days in both the pyridoxine as well as the control group.

There has been no evidence that those patients who required sedation, dietary, and other therapies for cures improved any more rapidly after the pyridoxine administration than those who did not receive it. It is possible that the dosage was inadequate but by comparison with the previous reports a sufficient amount was given.

It must not be forgotten that most patients became relieved of their nausea and vomiting about the end of the first trimester of pregnancy. Hence, any improvement may be spontaneous or natural. Certainly some patients are benefited by assurance. A fairly large number of these patients had had complications in previous pregnancies or attitudes during this one which might well be associated with an emotional imbalance. It is admitted that neurotic or psychoneurotic states might be major factors in the nausea and vomiting of pregnancy, but it is our conviction that the nausea and vomiting can be also on a physiologic or organic basis.

Summary

Every one of these sixteen patients was cured and the pregnancy carried on. It has not been necessary to perform a therapeutic abortion for hyperemesis in the Chicago Lying-in Hospital during the last few years. All staff cases and most of the private patients are treated by the routines outlined by Dieckmann.⁷

These observations reaffirm the need for proper controls in all clinical and therapeutic research just as it is necessary in the basic sciences. Since many factors can be involved in clinical studies, it does not become research until adequate and sufficient controls have been established.

A serious and earnest plea is advanced for critically controlled studies of all procedures and that publication be withheld until such controls are obtained.

Fortunately, pyridoxine can be given safely in these dosages (as far as we know now). Aside from the expense to the patient and delay in instituting therapy where cures did not follow, no particular damage can be claimed.

Another plea is offered for the retraction of prior recommendations when and as such corrections become evident to the original proponents.

Conclusion

Until factual evidence can be produced, it is proposed that pyridoxine in the dosages and methods used is of no more value in treatment of mild or moderate nausea and vomiting of pregnancy than scores of other preparations. On a percentage basis, better results were obtained by the administration of sterile water hypodermically and placebo tablets than by the use of pyridoxine. All the improvements can be explained readily on other bases.

The one patient with hyperemesis gravidarum of the entire series was cured only with the use of sedatives, and other measures. The use of pyridoxine as advocated in the literature for hyperemesis gravidarum is valueless and without justification.

This report does not imply that pyridoxine is not an essential vitamin but refers only to its use in the treatment of mild nausea and vomiting of pregnancy, as well as hyperemesis gravidarum.

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SULFATHIAZOLE IN THE CONTROL OF EPIDEMIC DIARRHEA OF THE NEWBORN

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A NEW plague has been visited on the human race, and its victims are the newborn infants. In 1933 the first outbreaks of epidemic diarrhea struck the nurseries of maternity hospitals and caused tremendously high fatalities and spread consternation among the hospital staffs. The health authorities began an extensive study of the disease to determine its cause and to attempt to check it. A great deal of work and research have been done, but unfortunately the organism has not been found, nor has the source of infection been determined. Rules and regulations for the newborn nurseries have been formulated to help reduce the frequency of the outbreaks and to prevent the spread of the disease. But in spite of all rules and regulations being followed, and proper precautions being taken, the disease continues to recur. It evidently is a new disease which has come to stay and plague us and is much more prevalent than the published reports would indicate.

I will not go into all the phases of the disease as they have already been well described and those who have seen cases are familiar with its manifestations and are profoundly impressed with its seriousness. However, some doctors are totally unaware of the existence of this disease, so when they encounter the condition, they fail to realize its seriousness and thereby delay in instituting proper treatment, with the most serious consequences.

The treatment usually employed in diarrhea of childhood is not sufficient to check epidemic diarrhea, and to depend on it only delays the more effective treatment. I wish to stress here only one phase in the treatment of epidemic diarrhea. There is an adage which says, "God is good. He provides the remedy with the disease." This aptly applies to sulfathiazole and epidemic diarrhea of the newborn, as both have arrived about the same time. We have been using sulfathiazole with amazingly good results and consider it an almost specific remedy in this condition. The reason for its effectiveness in our cases is that we give the drug immediately at the first sign or symptom of the diarrhea.

This type of diarrhea quickly causes dehydration, great loss of weight, acidosis, and a general upset in the metabolism of the infant which soon becomes irreversible. To give the drug after this stage is apparently not as effective and cannot undo the damage already done, whereas if the sulfathiazole is given early and promptly, it halts the disease before any damage is done, and the infant remains well.

In the best-regulated hospitals and with all necessary precautions taken, the disease still breaks out. Now, with the shortage of help and the overcrowding due to the war situation, it is inevitable that the disease should be more prev-

alent. Or, the disease may have seasonal variations as do other contagious diseases of childhood, which may account for the present (1944-1945) increase. The fact remains that the disease is with us, and until we have more specific knowledge how to prevent an outbreak, we must use the best means available for its treatment.

Our nursery nurses are constantly on the alert for frequent or watery stools and have orders to report the condition to the house doctor immediately. The nurse has instructions to give the baby a dose of sulfathiazole from a stock solution even before the doctor arrives. The doctor then confirms the diagnosis and gives further orders. The stock solution we use is made up 1 grain to the teaspoonful (0.06 Gm. to 4 c.c.). The sulfathiazole is repeated, 1 grain every three hours. It is given with a medicine dropper or a teaspoon directly into the baby's mouth to assure that the baby gets the full dose. After only a few doses the diarrhea is usually under control without even changing the formula. If the diarrhea is not under control, then all food is withheld for about twelve hours and saline is given by elysis while the medication is continued. If a second case appears, the same treatment is given to that child. Besides, every baby in the nursery who has been exposed is given a dose (1 grain) of sulfathiazole as a prophylactic measure to prevent the spread of the disease.

If a baby who is ready to go home develops a loose or suspicious stool, a dose of the sulfathiazole is given to the baby, and the mother is given a bottle (60 c.c.) of the medicine to take home, with instructions to give the baby one teaspoonful every three hours. To insure that it takes the entire amount, the medicine is given in only one ounce of the formula and the rest of the formula is given afterwards. When a mother and baby leave the hospital, the mother is instructed to watch the stools and to telephone the hospital and her private physician if at any time frequent or watery stools occur. In this way we are forewarned of any outbreak of the disease and can institute treatment of the baby immediately and take necessary precautions at the nursery. To make certain that there is no delay in starting treatment, we have a member of the family come to the hospital for the medicine, and we instruct her how to give it, or we telephone to their druggist to make up the prescription. We consider the promptness in starting the treatment of the utmost importance and therefore do everything possible to avoid delay in treatment. The diarrhea is brought under control in less than twenty-four hours, and it is a relief to get a report that the baby is constipated. Whatever changes in the formula are made or not made are of secondary importance to the giving of the sulfathiazole promptly.

When treatment was not instituted promptly in the manner outlined, as happened when the diarrhea started at home and the family failed to notify us, or the doctor failed to recognize the condition, the baby developed all the classical symptoms of epidemic diarrhea with serious consequences. These incidents served as controls, demonstrating that the other cases which were checked by sulfathiazole would have developed similar symptoms.

We have not used sulfadiazine in epidemic diarrhea as we are reluctant to try anything else since sulfathiazole has served us so well. We have not had occasion to try penicillin.

By the above procedure we were able to control the diarrhea in the infants and prevent the disease from becoming epidemic in our nursery.

Summary

Sulfathiazole given promptly at the very onset of epidemic diarrhea in the newborn infant cures the disease in less than twenty-four hours and prevents its spread in the newborn nursery.

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1831 GRAND CONCOURSE

SULFANILAMIDE AND SULFATHIAZOLE ABSORPTION VIA RECTUM AND VAGINA

Further Studies

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WITH THE TECHNICAL ASSISTANCE OF

M. A. HANNAH, M. T., AND CAMILLA BRADFORD, M.T.

RECENTLY there was reported from our laboratory a study¹ of sulfanilamide absorption via the vagina and rectum when the drug was given as a dry powder in a single weighed dose at the completion of operation on those viscera. In that study a constant amount of the drug, 5.9 Gm. (90 grains), was used in each case. Absorption was found to be fairly dependable but variable. We stated in that communication that it was our clinical impression that patients receiving the drug averaged a smoother convalescence than those who did not get it. We also felt that the presence of the drug in the vagina added a safety factor for patients having total hysterectomies, whether by the vaginal or abdominal route.

The known greater potency of sulfathiazole against some organisms made it desirable to study that drug also. Sulfanilamide had the generally better reputation in wounds and in the peritoneal cavity because of its lesser tendency to cake and lump in those localities, but we did not know how sulfathiazole would act in the rectum or vagina. There had also been considerable use by various surgeons of a mixture of sulfanilamide and sulfathiazole in wounds and in the peritoneal cavity. We did not know of any studies concerning the absorption of sulfathiazole or a mixture of the two sulfonamides from the vagina and rectum. We were interested also in determining whether the amount of sulfonamide used in the previous study was the optimum. It had been adopted as a safe initial twenty-four-hour dose on the basis of approximately 1 Gm. or 15 grains every four hours for six doses. Finally, we wondered how absorption from these viscera would compare with absorption from some enclosed area such as the peritoneal cavity. We were quite sure that, as a rule, not all of the drug was being absorbed from either viscera in our studies. The variations were so great that we did not wish to run the risk of too high concentration in the occasional patient by whom it was rapidly absorbed. Consequently we decided to check the vaginal and rectal absorption against the peritoneal as presumably all the drug would be absorbed from the peritoneal cavity.

From the new study, the following questions about the use of these two sulfonamides in the rectum and vagina were formulated:

1. How does absorption of sulfanilamide from the vagina and rectum compare with the absorption from the peritoneal cavity?
2. Does the absorption of sulfanilamide vary in proportion to the amount of drug used in the rectum and vagina?

3. Is sulfathiazole absorbed in similar manner from these viscera?

4. How is a mixture of these two sulfonamides absorbed?

5. What effect does the physical state of the drugs, i.e., whether introduced as a dry powder or as a paste, have upon their absorption?

The sulfanilamide determinations were run with the La Motte sulfonamide outfit.

The sulfanilamide and sulfathiazole mixed were determined with 0.15 c.c. of blood. This gave the same percentage as the determination of each sulfonamide separately as found by previous tests.

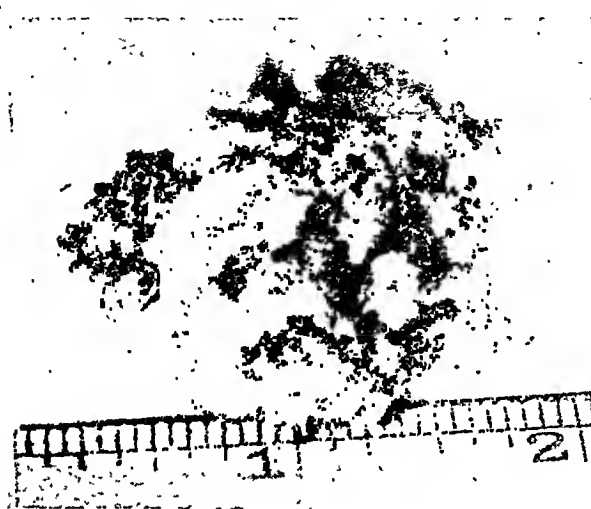


Fig. 1.—Hard cake of mixed sulfanilamide and sulfathiazole removed from the vagina fifty-six days after a mixture of the dry powders had been placed in the vagina at operation.

Question 1.—How does absorption of sulfanilamide from the vagina and rectum compare with its absorption from the peritoneal cavity?

Table I, when compared with our previous findings, showed a definitely higher and more constant level of the drug in the blood after intraperitoneal use than after rectal or vaginal administration.

Question 2.—Does the absorption of sulfanilamide vary in proportion to the amount of drug used?

Table II shows that within the limits of the previously recognized variations of absorption, the blood levels of the drug do vary directly with the amount of the dry powder placed in the rectum.

Table III, however, reveals a different story concerning vaginal absorption. Here, when the amount of dry drug was increased, the blood levels were less during the first two days after operation. Later, there was a rise as compared with the findings in our previous study when less drug had been used. Apparently moisture was the factor concerned. With more of the dry drug there was not sufficient moisture to get it into solution for early absorption.

Question 3.—Is sulfathiazole absorbed in similar manner from these viscera?

Tables IV and V show that a similar variable absorption of sulfathiazole takes place from the rectum and vagina. The blood levels do not appear significantly different from those obtained when using sulfanilamide.

Question 4.—How is a mixture of these two sulfonamides absorbed?

Tables VI and VII show that mixing the drugs appears to have little effect upon their absorption, though the blood level after rectal administration was somewhat less than for either of the drugs when given singly.

TABLE I. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER INTRAPERITONEAL ADMINISTRATION

HOSP. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22029	197	Sulfanilamide paste		9	Abdomen	9	4.5	4	Tr.	2	1.5	1.5	2.5	Tr.	Tr.
22041	172	Sulfanilamide paste		11.2	Abdomen	7	4	1.5	Tr.	3	Tr.	3	Tr.	2.2	Tr.
22108	154	Sulfanilamide paste		5.8	Abdomen	3	1.5	Tr.	3	0					
22096	114	Sulfanilamide paste		5.8	Abdomen	3	2	Tr.	3						
22103	153	Sulfanilamide paste		5.8	Abdomen	8	3	Tr.	Tr.						
22126m	117	Sulfanilamide paste		5.8	Abdomen	4	2	0							
22396	179	Sulfanilamide paste		8.4	Abdomen	Tr.	1.3	0	2.6	2.6	5.2	1.9	1.9	1.3	0
22420	150	Sulfanilamide paste		5.8	Abdomen	6	0	5	2	0					
Average				6.2		5	2.3	1.3							

In the tables the blood findings are reported in milligram per cent (mg. %) of sulfanilamide. Periods left blank mean that no tests were made at those times. "0" means that blood tests were done and failed to show any sulfanilamide present. "Tr." means trace present in insufficient amount for accurate determination—approximately less than 0.5 mg. per cent.

TABLE II. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22004	92	Sulfanilamide powder		5.8	Rectum	6	6	4	5	0.5					
21992	160	Sulfanilamide powder		11.2	Rectum	12	3.5	3.5	3.5	Tr.					
22001	118	Sulfanilamide powder		5.8	Rectum	2	1	0.5	1	Tr.	Tr.				
22014	174	Sulfanilamide powder		11.2	Rectum	1	3	3	1	Tr.					
22030	120	Sulfanilamide powder		9	Rectum	3	4	2	1	Tr.	1	Tr.			
Average				8.6		5.8	3.5	2.8	2.3						

TABLE III. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER ADMINISTRATION AS DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22008	165	Sulfanilamide powder		11.2	Vagina	0.5	5.5	3	Tr.	Tr.	1.5	Tr.			
22013	150	Sulfanilamide powder		11.2	Vagina	0.5	1	Tr.	3	Tr.	2	Tr.			
22024	118	Sulfanilamide powder		7	Vagina	Tr.	Tr.	Tr.	3	1.5	Tr.	1	Tr.	2	Tr.
22187	92	Sulfanilamide powder		5.8	Vagina	0	0	1.5	1.5	1.5	1.5	0			
Average				8.8		0.25	1.4	1.1	1.6						

TABLE IV. SULFATHIAZOLE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION AS A DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22023	200	Sulfathiazole powder		8	Rectum	1.5	4.5	5.2	1.5	4.5	2.2	Tr.			
22035	96	Sulfathiazole powder		5	Rectum	3	9.6	Tr.	1.5	3	2.5	1.5			
22078	152	Sulfathiazole powder		5.8	Rectum	Tr.	1	Tr.	Tr.	Tr.	1	0			
22125	175	Sulfathiazole powder		9	Rectum	Tr.	5.9	Tr.	2.2	0			1.5		
22138	219	Sulfathiazole powder		8.4	Rectum	Tr.	1.5	1.5	0.7	2.2	0				
22150	155	Sulfathiazole powder		5.8	Rectum	0	0	0	0				0		
22158	145	Sulfathiazole powder		5.8	Rectum	Tr.	0	1.4	0						
22166	141.5	Sulfathiazole powder		5.8	Rectum	Tr.	0	0							
22180	141.5	Sulfathiazole powder		5.8	Rectum	Tr.	0	0							
Average						0.5	3.5	0.9							

TABLE V. SULFATHIAZOLE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION AS DRY POWDER

HOSP. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22022	114	Sulfathiazole powder		6	Vagina	4.4	1.5	Tr.	Tr.	Tr.	Tr.	1.5			
22064	123	Sulfathiazole powder		5.8	Vagina	Tr.	Tr.	Tr.	Tr.	0					
22122	178	Sulfathiazole powder		8.4	Vagina	1.5	Tr.	0	0						
22129	154	Sulfathiazole powder		8.4	Vagina	5.9	0	0							
22135	163	Sulfathiazole powder		5.8	Vagina	1	0	Tr.	Tr.						
22143	165	Sulfathiazole powder		8.4	Vagina	Tr.	0		0						
22155	125	Sulfathiazole powder		5.8	Vagina	Tr.	0	0.7							
Average						6.9	1.8								

TABLE VI. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A DRY POWDER

HOSE. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22243	140	Sulfanilamide powder		5.8	Rectum	1.5	2.3	3	0						
22270	183	Sulfathiazole		8.4	Rectum		0	1.5	0						
22354	150	Sulfanilamide powder		5.8	Rectum	1	0	0							
22359	102	Sulfathiazole		5.8	Rectum	1.5	Tr.	0	2	2.5	2				
22410	205	Sulfanilamide powder		8.4	Rectum	2	1	1	0.5	4	0				
22408	135	Sulfathiazole		5.8	Rectum	1.5	1	1.5	0	6	1.5				
Average				6.7		1.25	0.7	1.1							

TABLE VII. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A DRY POWDER

HOSE. NO.	WT. (LB.)	DRUG AD-MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22192	143	Sulfanilamide powder		5.8	Vagina	5	1	0.5	0						
22151a	143.5	Sulfathiazole		5.8	Vagina	0.5	0	0							
22350	165	Sulfanilamide powder		8.4	Vagina	0	1	0	0						
22353	135	Sulfathiazole		8.4	Vagina	1	1	0	0						
22385	133	Sulfanilamide powder		5.8	Vagina		1	0	0						
22387	115	Sulfathiazole		8.4	Vagina	1	0	0							
22356	122	Sulfanilamide powder		8.4	Vagina	2	2.4	2	2	1.5	2	2.5	0.5	0	0.5
22371	130	Sulfathiazole		5.8	Vagina	4	4	2	1.5	1	0	0	3	1	1.5
22406	148	Sulfanilamide powder		5.8	Vagina	3	2	1	2	0.5	3.5	0.5	2	1.5	0.5
Average				6.9		1.3	1.3								

TABLE VIII. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER RECTAL ADMINISTRATION OF EQUAL PARTS SULFANILAMIDE AND SULFATHIAZOLE AS A PASTE

NO.	WT. (LB.)	DRUG AD- MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22544	160	Sulfanilamide paste Sulfathiazole (paste)		8.4	Rectum	6	2.5	2	1.5	3	1.5	2			
22560	146	Sulfanilamide paste Sulfathiazole (paste)		5.8	Rectum		2	2.5	1.5	2.5	1.5				
Average				7.1		4.7	2.2	2.2							

TABLE IX. SULFANILAMIDE CONCENTRATION IN BLOOD AFTER VAGINAL ADMINISTRATION OF EQUAL PARTS OF SULFANILAMIDE AND SULFATHIAZOLE AS A PASTE

HOSP. NO.	WT. (LB.)	DRUG AD- MINISTERED	PHYS. STATE	AMT. DRUG (GM.)	GIVEN PER	MG. % (6 HR.)	MG. % (24 HR.)	2	3	4	5	6	7	8	9
22443	100	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1.5	1	1	0.5	1	1	0			
22444	129	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1.5	1	1	1	Tr.	1.5	0	0		
22450	148	Sulfanilamide paste Sulfathiazole		5.8	Vagina	4.5	1	0.5	0	1	0	0			
22445	155	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1	1	1	Tr.	1	0	0			
22468	119	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1	1		0	0					
22526	128	Sulfanilamide paste Sulfathiazole		5.8	Vagina	3	2	1.5	1	0	2	2	1	1.5	1
22538	155	Sulfanilamide paste Sulfathiazole		8.4	Vagina	1.5	1.5	0	2	1.5	1	1.5	1.5	2	2
22552	100	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1.5	1.5	1.5	2	1.5	2.5	0.5	1.5	0.5	1.5
22561	125	Sulfanilamide paste Sulfathiazole		5.8	Vagina	1	1.5	1.5	1	2.5	1.5	1	2.5	0.5	1
22589	150	Sulfanilamide paste Sulfathiazole		5.8	Vagina	2.5	3	1	1						
22580	100	Sulfanilamide paste Sulfathiazole		5.8	Vagina	2	2.5	1.5	2						
Average				6.36		1.6	1.55	1							

Question 5.—What effect does the physical state of the drugs, i.e., whether introduced as a dry powder or as a paste, have upon their absorption?

Tables VIII and IX, when compared with Tables VI and VII, indicate that the mixed drugs are definitely better absorbed when introduced into the vagina or rectum as a moist paste than they are when introduced as a dry powder.

It should be noted in this connection that a mixture of equal parts of sulfanilamide and sulfathiazole goes through an interesting process as water is added to it. It gradually becomes moist and looks as though it were going to form a paste. Then it rather suddenly stiffens up and resembles partially set plaster. After a little more water has been added it again becomes a soft, moist paste. From one patient into whose vagina a mixture of the dry powders was placed at operation, a firm cake was removed when she returned for checkup eight weeks later (Fig. 1). Her blood had shown a minimal absorption of the drug. (See History No. 22353, Table VII.) The powders in this case had evidently been moistened only sufficiently to get to the plaster stage.

Since completion of this study, we have used these drugs vaginally in the treatment of a few cases of gonorrheal infection with excellent results. Our contact with such cases is rather limited but on theoretical grounds the vaginal use should give higher local concentration than would be obtained with similar blood levels after oral administration.

Summary

Sulfanilamide and sulfathiazole, separately or together, are absorbed variably from the rectum and vagina.

The absorption is hastened when the drug is inserted as a moist paste.

A mixture of the two drugs should be moistened beyond the "plaster" stage when used in the vagina.

It is suggested that local gonorrheal infections in women might be treated advantageously with sulfonamides via the vagina.

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ARE ANTIHORMONES FORMED DURING PREGNANCY?

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IT IS well known that antigonadotrophins may form in the blood stream of patients to whom gonadotrophic therapy has been administered.¹ However, these therapeutic measures frequently involve the injection of extracts of heterologous source and thus the formation of antagonistic substances might be anticipated. An unusual situation is created by pregnancy for during this time there is a marked and continuous production of chorionic gonadotrophin and, while this substance is of homologous source, it is nevertheless adding a new substance to the blood stream. Optimal conditions for the spontaneous development of antihormones are presented by pregnancy, and limited tests have been made during this period and up to one month after parturition for the detection of antagonists in the serum against pregnancy urine extracts, but all were negative.²⁻⁵ Extended treatment of patients with chorionic gonadotrophin has also failed to cause antihormone formation. For example, Dorff⁶ administered as much as 112,300 R.U. over a seventeen-month period and during this time antigonadotrophins did not appear.

Although it would appear that antihormones against pregnancy urine extracts do not develop during pregnancy, the fact that a prolonged amenorrhea occurs in some cases following parturition led us to reinvestigate the antihormone problem. It seemed more logical to consider the formation of antagonists against the pituitary as a possible etiology of the amenorrhea. Fluhmann² did test post-partum serum against human pituitary in one case but failed to detect antihormones. Therefore, in view of the paucity of data concerning the antihormone formation during pregnancy we are presenting the data from ten cases in which the sera were tested for antigonadotrophins against both chorionic gonadotrophin and human pituitary.

Procedures and Results

Blood was obtained from 8 patients four weeks post partum and from 2 patients two weeks post partum. The blood was permitted to clot, the serum separated, centrifuged, and stored in an ice chest until and during the test period. All sera tests were started within seventy-two hours after the blood was drawn.

To test for antihormones against chorionic gonadotrophin, 22-day-old female mice were used. All test mice received a total of 40 I.U. of chorionic gonadotrophin in equally divided daily doses and, at a different site, a total of 0.9 c.c. of the serum to be tested. Injections were made subcutaneously once daily for three days and the mice killed seventy-two hours after the first injection. The weights of the ovaries and uteri were obtained at autopsy, the later after removal of intrauterine fluid. Two to four mice were used for each serum test and this response was compared with two litter mates injected with chorionic gonadotrophin alone.

TABLE I. ANTIGONADOTROPHIC TESTS IN MICE WITH POSTPARTUM SERA

SERUM FROM PATIENT	CHORIONIC GONADOTROPIN (I.U.)	SERUM (C.C.)	AVERAGE OVARIAN WT. (MG.)	AVERAGE UTERINE WT. (MG.)
E. G.	40	0.9	7.2	29
V. B.	40	0.9	10.3	27
C. J.	40	0.9	8.2	30
D. H.	40	0.9	9.3	27
B. W.	40	0.9	8.9	31
A. B.	40	0.9	9.9	30
E. W.	40	0.9	7.5	17
E. S.	40	0.9	7.5	29
H. D.	40	0.9	8.1	46
R. H.	40	0.9	8.7	47
<i>Control Experiments</i>				
	40	None	8.8	34
	None	None	3.0	6

Antihormone tests for antagonists against human pituitary were performed in the manner described but in this case 22- to 24-day-old rats were used instead of mice. The human pituitary material was acetone dried and administered in 2 mg. quantities. The pituitary powder was macerated in a centrifuge tube with a small amount of distilled water and after making the desired dilution was injected as an extract and suspension. The 2 mg. dosage produced a marked and uniform ovarian stimulation.

An inhibitory serum can readily be detected by its ability to nullify the gonad-stimulating capacity of a uniform dose of a gonadotrophic hormone. Table I illustrates that none of the ten sera examined gave reason to suspect the presence of antihormones against chorionic gonadotrophin. A marked increase in ovarian weight resulted with the dosage of hormone used and this stimulating action was not influenced by the simultaneous administration of postpartum serum. Similar results were obtained with human pituitary. A pronounced ovarian weight increase was obtained with the human pituitary material but the gonadotrophic activity was not impaired by concomitant serum administration. (Table II.)

TABLE II. ANTIGONADOTROPHIC TESTS IN RATS WITH POSTPARTUM SERA

SERUM FROM PATIENT	HUMAN PITUITARY (MG.)	SERUM (C.C.)	AVERAGE OVARIAN WT. (MG.)	AVERAGE UTERINE WT. (MG.)
E. G.	2	0.9	53	76
V. B.	2	0.9	120	112
C. J.	2	0.9	50	82
D. H.	2	0.9	64	155
B. W.	2	0.9	71	115
A. B.	2	0.9	57	89
E. W.	2	0.9	69	80
E. S.	2	0.9	70	150
H. D.	2	0.9	55	117
R. H.	2	0.9	62	181
<i>Control Experiments</i>				
	2	None	61	111
	None	None	13	32

In agreement with previous reports, therefore, we did not find antihormones against chorionic gonadotrophin in postpartum serum. Furthermore, our tests for antigonadotrophins against human pituitary were negative. On the basis of the evidence at hand we cannot subscribe to an antihormonic cause for amenorrhea following parturition. We have used 0.9 c.c. of serum

routinely in testing for antihormones and this amount can be contested as insufficient. However, previous experience has indicated that definitely inhibitory sera can readily be detected with the 0.9 c.c. quantity.^{7, 8}

Summary

The sera from 10 patients, two to four weeks postpartum, were tested for the presence of antigonadotrophic substances against chorionic gonadotrophin and human pituitary. All tests were uniformly negative. Thus gonadotrophins of homologous source are not antigenic and no evidence is available for an antihormonic cause of amenorrhea following parturition.

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ETHINYL ESTRADIOL IN THE TREATMENT OF METRORRHAGIA

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THE induction of cyclic bleeding in the anovulatory type of metrorrhagia by the cyclic administration of estrogen-progesterone was originally advanced by Hamblen.¹ His observation that the functional bleeding of adolescence could be satisfactorily controlled by the administration of the estrogens was subsequently confirmed by this author, who reported upon the use of cyclic stilbestrol-progesterone in the treatment of these patients.² The evidence is now adequate to permit a dogmatic statement on the efficacy of the estrogens in the control of functional bleeding. So specific is the administration of the estrogens in large doses, that complete cessation of uterine bleeding may be expected in approximately 80 per cent of the patients with anovulatory functional bleeding within a period of seventy-two hours, following the daily administration of stilbestrol (5 mg.) every twenty-four hours. A serious objection to the use of such large doses of stilbestrol is to be found in the high incidence of nausea which it produces. It is a tragic sequence when a patient, being already partially exsanguinated, is unable to receive benefit of therapy because of her failure to tolerate the drug. A second objection to stilbestrol therapy is based on the fact that it is a sterol derivative whose chemical structure has little similarity to estradiol. On purely hypothetical grounds, it would seem that the administration of an estrogen chemically akin to that which the human body is accustomed to metabolize should be more acceptable. Until a recent date the natural estrogens and the synthetic estradiols were available for oral administration in a dosage form which made them practical for the treatment of the climacteric where small doses are adequate, but totally impractical for the control of metrorrhagia where large oral doses are necessary. A synthetic estrogen, chemically similar to natural estrogen and sufficiently potent when administered orally, has been made available in the form of ethinyl estradiol. It has been shown by Willard Allen that this estrogen is 26 times as potent as hexestrol, and 7.5 times as potent as diethylstilbestrol.³

Clinical Material Comprising Study

In order to compare the hemostatic effect of ethinyl estradiol with previous experience using diethylstilbestrol, a group of twelve patients suffering with anovulatory functional bleeding were studied. All of these patients were partially exsanguinated from prolonged, intermittent, uterine bleeding, the hemoglobin ranging from 24 per cent (Sahli) to 60 per cent. From each patient, an endometrial biopsy was obtained before starting treatment. In each case, the endometrium showed a persistent proliferative phase which varied from moderate atrophy to marked hyperplasia. The degree of endometrial atrophy or hyperplasia is not necessarily related to the amount or duration of bleeding.

Careful examination of these case reports will reveal that the most persistent uterine bleeding is found in those cases with atrophy of the endometrium, while those with hyperplasia are more readily controlled. In each of these patients, the endometrial biopsy was repeated at intervals of one week for periods of time varying from two weeks to five weeks. Another biopsy was obtained upon completion of the treatment, and in seven cases a follow-up biopsy was taken six months after completion of all treatment. The average number of endometrial biopsies for the entire group was six per patient. At the same time that each endometrial biopsy was taken, a vaginal smear was obtained by aspiration and stained for study of the glycogen content and degree of keratinization of the vaginal epithelium.

Treatment Program

Following the confirmation of diagnosis by endometrial biopsies, all patients were placed on the same treatment program. They were given a 0.3 mg. of ethinyl estradiol (6 tablets of 0.05 mg. each) daily at bedtime for twenty nights. On each of the last five days of the ethinyl estradiol, each patient also received 5.0 mg. of progesterone by hypodermic injection. Both ethinyl estradiol and progesterone treatment were discontinued on the twentieth day, and in every case of estrogen-progesterone withdrawal, bleeding occurred within one to six days after cessation of treatment. On the fifth day from the onset of this induced bleeding episode, the twenty-day treatment of ethinyl estradiol, supplemented by progesterone on the last five days, was repeated. Again, all treatment was stopped, and a third cycle of treatment was instituted. In other words, after the bleeding had been controlled by twenty days of estrogen-progesterone treatment, and the induced bleeding episode had occurred, then the patients were instructed on printed instruction sheets to take six tablets daily at bedtime from the fifth to the twenty-fifth day of the menstrual cycle. They were instructed to come to the clinic on the twentieth, twenty-first, twenty-second, twenty-third, and twenty-fourth day of their cycle for an injection of progesterone. (All cases are not reported in detail because of the paper shortage which necessitates editorial limitation.) A typical case is reported:

M. R. B., aged 16 years.

April 8, 1944.—Menses began at 12 years of age, followed by several scanty menses at long intervals over a period of two years; during the last year, menstrual periods averaged from three to five weeks in duration. Flow has never been excessive in amount, but the duration has been such as to make it necessary for the patient to wear a pad most of the time. Endometrial biopsy: Hyperplastic proliferative phase; tendency to polypoid formation. Vaginal smear: 4 + keratinization; 1 + superficial cells; no basal cells; no leucocytes; 4 + blood.

April 17, 1944.—Bleeding has persisted since last examination. Endometrial biopsy: polypoid hyperplastic proliferative phase. Vaginal smear: 4 + keratinization; 1 + superficial cells; 4 + blood. Twenty-day treatment of ethinyl estradiol plus progesterone started.

May 1, 1944.—All bleeding stopped after the third day of treatment. Slight nausea occurred as a result of ethinyl administration. Patient was made to persist in taking it. Endometrial biopsy: polypoid hyperplastic proliferative phase. Vaginal smear: 4 + keratinization; 1 + superficial cells; no blood; no leucocytes.

May 6, 1944.—Treatment stopped.

May 11, 1944.—Menstruation began. Flow was normal in amount. No dysmenorrhea.

May 15, 1944.—Ethinyl-estradiol-progesterone twenty-day treatment resumed.

June 4, 1944.—Treatment stopped.

June 6, 1944.—Menstruation began, normal in amount and duration. Endometrial biopsy: secretory phase. Vaginal smear: 4 + keratinization; no superficial cells; no basal cells.

This patient was followed over a period of four months after completing three cycles of treatment, and she continued to have normal cyclic uterine bleeding. Each endometrial biopsy showed a normal secretory phase. One cannot attribute to therapy the transition of this patient from the anovulatory to the ovulatory because this may have been the result of normal physiologic maturity not related to the treatment.

Summary

Irregular bleeding, acyclic bleeding from the uterus, must first be classified according to etiology. Approximately one-half of the patients seen in private practice with this complaint have an organic basis for that bleeding. The other half bleed from the uterus as a result of abnormal physiology in the pituitary-ovarian endometrium cycle. This latter group must be further classified into two groups. Those who bleed from a secretory phase endometrium are essentially normal endocrinologically in that the prime prerequisite for normalcy is present, namely, the maturation of the follicle with the extrusion of the ovum and development of the corpus luteum, followed by normal endometrial response. The patients in whom the bleeding comes from a proliferative phase endometrium are candidates for treatment by endocrine therapy.

Bleeding can be controlled satisfactorily by the administration of large oral doses of the estrogens. Use of estrogen-progesterone over a period of three successive months will establish regular cyclic bleeding in about 90 per cent of anovulatory metrorrhagic patients while under treatment. Normal cyclic menstruation will continue in about 70 per cent of patients after discontinuing treatment. Of this latter group, about one-half of them will subsequently menstruate from a secretory phase endometrium, suggesting that the treatment not only controls the immediate bleeding, but may also establish normal, pituitary-ovarian-endometrial physiology. In that group which ovulates following treatment, it is obviously impossible to state that the ovulation was induced by therapy, since spontaneous recovery of ovarian function can occur in the absence of any treatment. However, the relatively high salvage in this group of cases of marked ovarian failure suggests the probability of a cause and effect relationship.

Summary and Conclusions

Ethinyl estradiol (0.3 mg.) was administered daily for twenty days to a group of twelve patients suffering from anovulatory metrorrhagia; the treatment was begun as soon as the diagnosis was established. All of these patients were partially exsanguinated from prolonged and excessive bleeding. Uterine bleeding stopped in all cases except one within six days after starting treatment. Progesterone (5 mg.) was administered daily by hypodermic injection on the last five days of ethinyl estradiol administration. When the ethinyl estradiol-progesterone twenty-day treatment was stopped, all patients menstruated within five days as a result of estrogen-progesterone withdrawal. On the fifth day from the onset of this induced bleeding episode, the twenty-day treatment was resumed, and another bleeding episode occurred in all patients within five days after completing the second cycle of treatment. A third cycle of treatment was instituted on the fifth day of this bleeding episode. In other words, the patients

were treated from the fifth to the twenty-fifth day of the menstrual cycle by ethinyl estradiol (0.3 mg.) daily for 20 days, and progesterone (5 mg.) from the twenty-first to the twenty-fifth day of the menstrual cycle. All of these patients were followed by repeated endometrial biopsies and vaginal smears during the treatment. A follow-up of from three to twelve months after treatment was presented.

Ethinyl estradiol in oral dose of 0.3 mg. is comparable to diethylstilbestrol in oral dose of 5 mg. in so far as control of anovulatory bleeding is concerned. Only one patient complained of nausea from the ethinyl estradiol, and this was not troublesome. The incidence of regular cyclic bleeding following ethinyl estradiol is about the same as in a previously reported group treated with diethylstilbestrol. However, the ovulation salvage in the ethinyl estradiol group (35 per cent) was distinctly better than that in the diethylstilbestrol treated group (16 per cent).

Estinyl (ethinyl estradiol) and progesterone (proluton) supplied through the courtesy of Dr. William R. Bond of the Schering Corporation.

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PUERPERAL STERILIZATION

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DURING the past four years 51 puerperal sterilizations have been performed on the obstetric services at the Sloane Hospital for Women. This small group of cases will be reviewed and compared with the ten series of similar cases reported in the American literature up to December, 1944.

Skajaa¹ was one of the earliest advocates of puerperal sterilization. In 1932 he reported on 46 cases. In 1939 Adair and Brown² reviewed 50 cases, the first series to appear in the American literature. Since then ten additional series have been reported.³⁻¹²

The first puerperal sterilization at Sloane Hospital was performed in 1938. Since then the number of such operations has increased every year as follows:

		1941	6
1938	1	1942	10
1939	1	1943	10
1940	6	1944	17

The number of viable births in 1942, 1943, and 1944 was 1,680, 1,859, and 1,964, respectively. Our incidence of postpartum sterilizations in terms of viable births for these three years was 0.59 per cent, 0.54 per cent, and 0.85 per cent. Our indications for performing this operation follow closely those outlined by others.^{2, 8, 9} Table I lists the indications. By multiparity we include only those patients having three or more living children at the time of performing this operation. The entire group had a total of 186 living children out of a total of 299 pregnancies.

Their ages ranged from 21 to 42 years. The average was 32.8 years.

The Pomeroy sterilization was used exclusively.

The average follow-up for all patients operated on prior to 1944 was 14.7 months.

The one known failure in this series has been reported in another communication.*

The operations were performed between the first and the tenth postpartum days. The distribution and morbidity rate, based on the standards set by the Committee on Maternal Welfare, are shown in Table II. Twenty-three, or 46 per cent, of the patients were entirely afebrile throughout their puerperium.

Postoperative complications included two cases of thrombophlebitis, one severe upper respiratory infection, one nonfatal pulmonary embolism, one hematoma of the broad ligament, one minor wound infection, and one wound hematoma.

*AM. J. OBST. & GYNEC. (later Issue).

TABLE I. INDICATIONS FOR PUERPERAL STERILIZATION

Rheumatic heart disease	9
Recurrent toxemia	9
Recurrent pyelonephritis	2
Multiparity	35
Epilepsy	2
Recurrent hyperemesis	2
Bronchiectasis	1
Poliomyelitis deformity	1
Psychosis	3
Tertiary syphilis	1
Hypertension	3
Hypertrophy of breasts	1
Congenital cystic disease of lungs	1
Multiple sclerosis	1
Erythroblastosis, recurrent	1

TABLE II. PUERPERAL STERILIZATIONS, TIME OPERATION PERFORMED AND MORBIDITY

DAY OF OPERATION	NO. OF PATIENTS	NO. FEBRILE	PER CENT
1	1		
2	2		
3	12	3	25.0
4	16	3	18.7
5	10	3	30.0
6	6	1	16.6
7	1		
8	1		
9	1		
10	1		
Total	51	10	19.7

No routine type of anesthesia was used in this series. Pentothal sodium intravenously, nitrous oxide with oxygen and ether, and local novocain were used, depending on the patient's medical condition.

A short vertical incision and absorbable suture material were used throughout.

In this series there were five medical inductions of labor. In ten cases the membranes ruptured before the onset of labor, two to twelve hours before delivery. Three low forceps deliveries were performed. There was one case of prolonged labor. In another patient manual removal of the placenta was necessary. One patient had a curettage and tamponade of the uterus on her fourth postpartum day because of retained secundines. This delayed postpartum sterilization until her tenth day. Only two of these cases were morbid, namely, one of the low forceps deliveries, and one patient who had a fifty-two-hour labor.

In six instances the resected tubal fragments revealed either a mild subacute or acute endosalpingitis. Only one of these patients was febrile.

The average period of hospitalization for these patients was about fifteen days.

Discussion

A survey of the reported series of puerperal sterilizations reveals many individual variations (Table III). Considerable discussion has revolved around the question of immediate or delayed operation. Skajaa¹ chose the third and fourth postpartum days as the optimal time for sterilization. Adair and Brown²

TABLE III

AUTHOR AND YEAR	AVERAGE AGE (YR.)	AVERAGE PARITY	TECHNIQUE	AVERAGE TIME OPERATION PERFORMED P.P.	PER CENT MORBIDITY	COMPLICATIONS	MATERNAL MORTALITY	FOLLOW-UP (%)	NUMBER OF CASES	FAILURES	ANESTHESIA	TOTAL HOSPITAL DAYS	INCIDENTAL SURGERY
Stajna ¹ 1932	37.1		Cornual resection	5 days		8 thromboses			126		114 local 12 ether		
Adair and Brown ² 1939	29.5	4.6	Madlener	11.5 hours	12	1 embolism 6 thromboses	0		50	0	Local	11.3	
Russell ³ 1940		5		2 hours		1 abscess	0		29			10	
Amundsen ⁴ 1940	35.8	5.8	Cornual resection	5 days	10.8	6 thromboses			150	0	Local		
Howitt and Whitely ⁵ 1940	31	5.5	Modified Madlener	1 hour	2	1 sepsis 1 pyelitis			100		General	9.4	
Pfuetze ⁶ 1941	27.8	5	Madlener	17.5 hours	18.3	2 phlebitis	0		165	3	Local	9.4	3 herniorrhaphies
Thornton ⁷ 1941	29.4	6.6 for 175 patients	219 Pomeroy 86 Resections 3 Madlener	5 days	21	3 endometritis 3 pyelitis 2 pneumonias 1 embolus 1 phlebitis 1 atelectasis 1 diabetic coma	1	73	309	0	297 spinal 9 general 3 local	11.7	178 appendectomies
Mays and Dilworths 1941	28	5	29 Modified Madlener 2 Cornual	50% on 4th day	28	1 pneumonia 2 cystitis 3 endometritis 1 atelectasis 2 wound infections	0		31		Local	16.7	
Pirch ⁸ 1941	28.4	4.5	Resection	26 hours	2.8				35		Local	9.5	
Brennecke ¹⁰ 1941			Madlener						23				
Lock ¹¹ 1942		4.7	57 Pomeroy 2 Madlener		8.5	1 phlebitis 1 pyelitis 1 hematoma		54	59	2	Local	7.1 days after operation	1 appendectomy
Goldblatt ¹² 1943			Pomeroy	3rd day	30						Local		
Sloane 1944	31.9	5.8	Pomeroy	4.5 days	21.2	2 phlebitis 1 embolism 1 wound 1 hematoma 1 broad ligament	0	95	34	1	15 pentothal 19 gas-oxygen-ether	15.8	Excision 2 parovarian cysts

elected to perform their sterilization immediately after delivery. Others who believe in early operation include Pfuetze,⁶ Russell,³ Hewitt and Whitley.⁵ Pfuetze had a morbidity rate of 13 per cent for cases operated on within the first twenty-four hours as compared with 30 per cent for those done later. Adair and Brown's morbidity was 12 per cent, and Hewitt and Whitley's, 2 per cent. Other authors do not believe that the time of performance of this operation has any bearing on the incidence of postoperative morbidity. Among these are Mays and Dilworth,⁸ Goldblatt¹² and Thornton.⁷ Their morbidity rates were 28 per cent, 30 per cent, and 21 per cent respectively. Thornton's series is the largest. He performed puerperal sterilizations up to three weeks after delivery and found no correlation between the time of performance of the operation and febrile reaction. Thornton believes that the careful selection of patients is far more important with reference to morbidity than when the sterilization is performed. In our small series of cases there was no definite trend in morbidity which seemed totally unrelated to the day on which the operation was performed (Table II).

Skajaa's high incidence of thrombophlebitis and embolism was surely related to his high incidence of intrapartum manipulation in the preceding labor. A more careful selection of cases would undoubtedly have lowered his high morbidity. Adair and Brown² and Thornton⁷ emphasize the importance of this. However, it is inevitable that an occasional candidate for puerperal sterilization will develop some intrapartum complication necessitating either major or minor obstetric procedures. Whether or not such a procedure should contraindicate sterilization is a matter of judgment. Certainly, in such cases, one would be foolhardy in performing an early sterilizing operation without waiting a few days to determine whether or not she will develop an acute puerperal infection. Not a few cases of puerperal sepsis have followed perfectly normal labor and delivery. With these facts in mind it is our policy to perform this operation the fourth day when possible, by which time, in most cases, contraindications in the form of sepsis or endometritis will have become manifest.

The only advantage in early operation seems to be shortening of the patient's hospital stay. Our patients spent, on the average, fifteen days in the hospital. In many instances these patients had heart disease or toxemia which necessitated longer convalescence.

Of some interest is Thornton's 178 appendectomies, performed as incidental procedures at the time of puerperal sterilization. We do not feel that such a procedure is either indicated or justified. The only incidental surgery we performed was the removal of two parovarian cysts.

For the most part the type of anesthesia used seems to be a matter of personal preference. In our cases we used chiefly intravenous pentothal, or gas, oxygen, and ether.

Conclusions

1. Postpartum sterilization is a rational and safe procedure when indicated.

2. Cases for this procedure should be selected with care.

3. The fourth or fifth postpartum day is the safest time for performing this operation.

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PANHYSTERECTOMY WITHOUT VAGINAL CLEANSING*

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IN MANY gynecologic clinics special precautions are taken to cleanse and sterilize the vagina preliminary to panhysterectomy. Many operators have attributed the absence of operative infection in their cases to this procedure. In this clinic for many years it has been the practice to consider the vagina potentially infected and any complete sterilization impossible. Besides their presence in the vaginal secretions, organisms may be found below the surface between cells. The continuous extrusion of secretions from the cervix, and the peculiar anatomic configuration of the vagina with its many folds are some of the factors which make it impossible actually to sterilize the vagina.

Therefore, in this Clinic, abdominal panhysterectomies are performed without any vaginal preparation. Since we consider the vagina to be a septic focus, we believe it is wiser to adopt measures of isolation of the said focus rather than trust to a necessarily imperfect sterilization. The method we use to meet this aim will be made clear in the technique.

Technique of Operation

After anesthetization the patient is catheterized and re-examined vaginally to verify the preoperative diagnosis and the cervix is again inspected for pathology. No attempt whatsoever is made to cleanse or sterilize the vagina. Since clamps are not used, many of the operations are easily performed through a relatively small incision. We use the following method: Each vessel is doubly ligated, the ligatures are tied but are not cut. The catgut ends are brought out of the wound and held with hemostats; these can be used for traction in order to bring a bleeding vessel into better view if necessary in difficult cases. The ligaments and the bladder reflexion are then sectioned to uncover the uterine arteries. The bladder is pushed downward anteriorly and laterally below the cervix. The uterine vessels are then doubly ligated by passing the ligature carrier at right angles to the long axis of the uterus close to the cervix, at the level of the internal os, to avoid the ureters (Fig. 1). Moderate traction is made by an assistant on the ligatures of the uterine vessels while they are cut and pushed off the uterus with gauze.

The following technique to isolate the infected vagina is then applied meticulously; two sponges are placed in the cul-de-sac. A small incision is then made in the anterior fornix just above the palpated end of the cervix. An assistant immediately places an Allis forceps on the cut anterior vaginal wall and holds it vertically in order to prevent it from coming in contact with the surrounding tissues and to prevent any drip. The vagina is then cut close around the cervix. An open sponge is then introduced into the vagina with long forceps. Additional Allis forceps are placed on the cut vagina anteriorly, laterally, and posteriorly in order to maintain the vaginal cuff vertically and on stretch (Fig. 2). The vagina is then closed and the sponges from the cul-de-sac are removed. All instruments are discarded. The vaginal fascia is then sewed; the uterine vessels, the round and the infundibulopelvic ligaments

*Read at a meeting of the Philadelphia Obstetrical Society, Jan. 4, 1945.

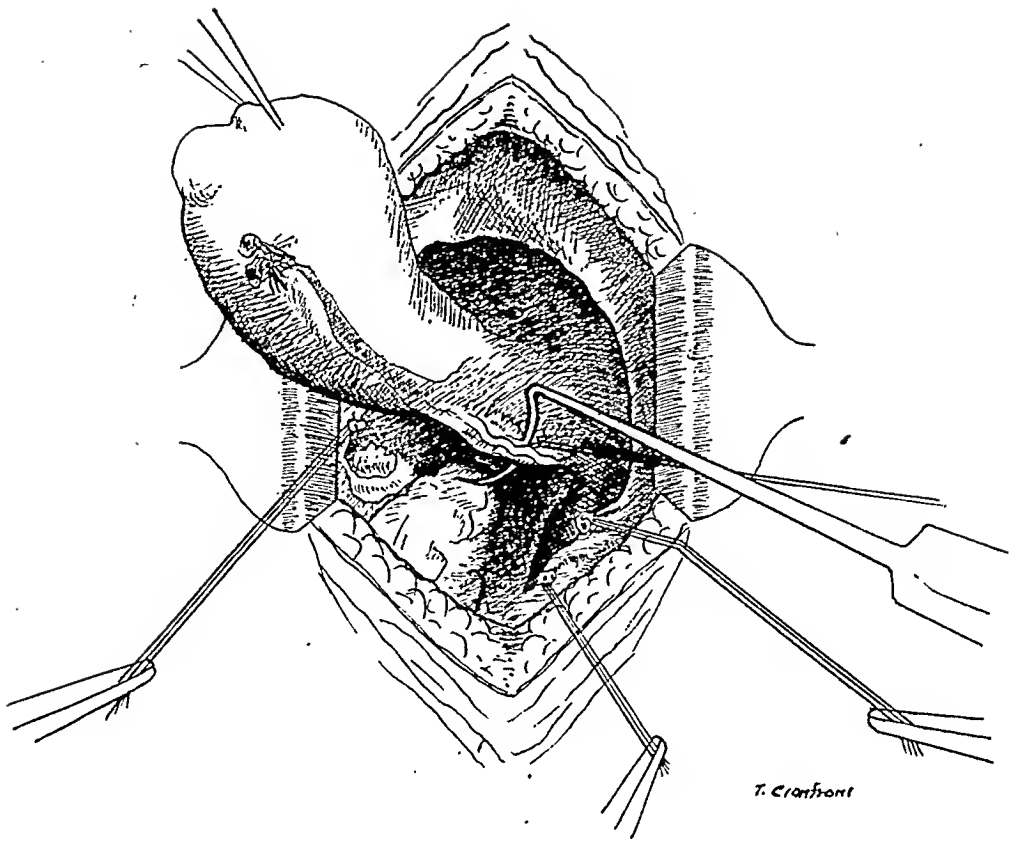


Fig. 1.—Showing the doubly threaded ligature carrier passed at right angles to the long axis of the uterus, and close to the cervix, to avoid the ureters.

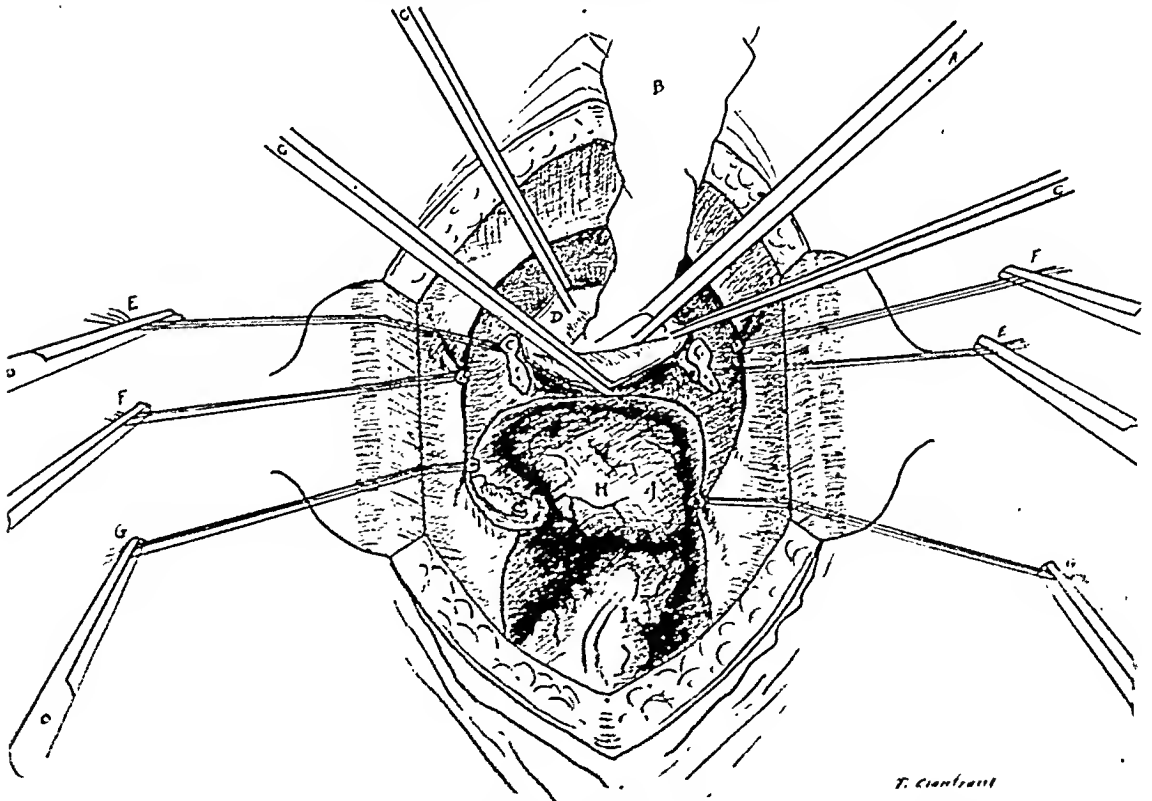


Fig. 2.—A, Long forceps; B, sponge; C, Allis forceps; D, vaginal cuff; E, ligature on the uterine vessels; F, ligature on the round ligament; G, ligature on the infundibulopelvic ligament; H, sponges in the cul-de-sac; I, rectum.
Allis forceps are placed on the vaginal cuff in order to maintain it vertically and on stretch. An open sponge is then introduced into the vagina with long forceps.

are retied; and the closure of the broad ligament is started at one infundibulopelvic ligament and continued to the one on the opposite side with a running suture. Neither abdominal nor pelvic drainage is used.

We are not including in this series the numerous cases of supravaginal hysterectomy with complete coning of the cervix done in this clinic. In these the technique of vaginal isolation, instead of attempts at sterilization, was used, and no peritonitis developed in any of them postoperatively.

Review of Cases

A thorough study of the charts of the 130 cases was made to ascertain facts that were pertinent to the operative results, and only these were recorded. The series consisted of 94 Negroes and 34 whites; 85 per cent were in the age group of 30 to 45 years; 53 of the cases had appendectomies done; and 27 had positive Wassermanns.

TABLE I. PATHOLOGIC CONDITIONS ENCOUNTERED

65	fibroids
23	fibroids and pyosalpinx
24	bilateral pyosalpinx
1	fibroid with endometriosis
4	fibroids with adenomyosis
3	fibroids with fundal cancer
2	fibroids with dermoid
1	granulosa-cell tumor of ovary
1	Krukenberg tumor of the ovary
4	ovarian cysts
1	bilateral solid carcinoma of ovaries
1	cyst of ovary with adhesions

130

It is to be noted that the cases included in this report were generally of a very serious nature, since most of our ward work is done on neglected cases, due to the social stratum from which these patients come.

TABLE II. TEMPERATURE ANALYSIS

GROUP	NO. OF CASES	DAY OF NORMAL TEMPERATURE	HIGHEST TEMPERATURE	DAY OF HIGHEST TEMPERATURE
A	101	5th	100.2° F. (99.2-102° F.)	2nd
B	14	8th	101.5° F. (101-104° F.)	5th
C	15	10th	102.8° F. (101-103° F.)	13th

We divided the cases into three groups, the figures used are the mean, calculated from the low and high of each group.

Group A.—Cases that had normal temperatures within the first week. There were 101 such cases; they had a normal temperature by the fifth day with the highest temperature of 100.2° F. on the second day.

Group B.—Cases that had fever for more than one week. There were 14 of these cases; they had a normal temperature by the eighth day, with the highest temperature of 101.5° F. on the fifth day.

Group C.—These were the cases with demonstrable complications. There were 15 cases; they had a normal temperature by the tenth day with the highest temperature of 102.8° F. by the thirteenth day. This is the only group that required extra hospitalization, being discharged on the twenty-fourth day on an average, instead of the usual sixteen to seventeen days.

TABLE III. COMPLICATIONS

6	severe wound infections
3	moderate wound infections
3	indurated broad ligaments
1	thrombophlebitis of the leg
1	pyelitis
1	cystitis

 15

We do not believe that appendectomies increased the operative risk in this series because, of the 15 cases with complications, only 6 had appendectomies, which is less than 50 per cent. The 115 cases with no complications contained 47 appendectomies, which is approximately the same proportion as found in the 15 cases with complications.

Positive Wassermanns did not affect the postoperative course in this series. There were many more negative than positive Wassermanns in the group with complications. Of the 27 positive Wassermanns in the entire series, only 3 occurred in the group of 15 cases with complications.

The presence of pelvic inflammatory disease may have had some influence on the postoperative course of our cases, because there were 8 cases of pelvic inflammatory disease in the 15 cases of complications, whereas there were only 39 cases of pelvic inflammatory disease in the 115 cases without actual complications. Included in these 115 cases are the 14 cases with a protracted fever for more than one week, but with no demonstrable complications; they showed the same proportion, namely, 5 cases of pelvic inflammatory disease in 14 cases.

Mortality.—There were two deaths, both from pulmonary embolism.

1. One occurred in a Negro woman, 38 years old, with bilateral intraligamentary fibroids. Her postoperative convalescence was uneventful until the fourteenth day, when she developed a pulmonary embolism and died. The autopsy showed a hemorrhagic infarct of the right lung, and acute pulmonary embolism, and thrombosis and embolism of the right internal iliac veins.

2. The second was in a white woman, 47 years old, with multinodular fibroids. Her postoperative convalescence was uneventful; she was out of bed on the fourteenth day. On the sixteenth day, before going home, she developed a pulmonary embolism and died. An autopsy was not obtained.

Discussion

The results in this series approximates other studies of panhysterectomies *with* vaginal sterilization. Most of the cases reported had diseased cervixes, and in this clinic a diseased cervix in a case that needs a hysterectomy always demands removal, except in some cases in which removal increases the operative risk. In these instances we must be content with a supravaginal hysterectomy with partial coning followed by cauterization at some future time, or hysterectomy with complete coning of the cervix. Unless the patient's condition militates against it, panhysterectomy is preferred even in cases with apparently normal cervixes. Our technique, in which we do not use clamps but instead cut around the vagina close to the cervix, minimizes the danger of a short vagina. Also, in patients in whom hysterectomy has been preceded by extensive plastics in which ligaments have been much disturbed, panhysterectomy may not be the procedure of choice. This preference for panhysterectomy instead of supravaginal operation in cases with apparently healthy cervixes is the result of repeated findings of cervical cysts deep and high up, noticed when cutting across the cervix in a supravaginal operation. These deep-seated cysts, and the at-

tendant infection that is nearly always present, are difficult to eradicate by the subsequent cauterization or electrocoagulation. Most important of all is the threat of cervical carcinoma, which always remains unless a panhysterectomy has been done, and we wish to emphasize that this is a real threat to the patient's future welfare, despite the fact that only three of our cases of supravaginal hysterectomies have returned to us with stump carcinoma; but we feel sure that a certain number of them have found, or will at some time find their way to some other clinic for this condition.

Because we believe the use of soap and water and the application of antiseptics vaginally prior to or at the time of operation will not sterilize the vagina, we have emphasized the technique which prevents peritoneal contamination rather than vaginal sterilization. We further believe from long experience that the sponge which is introduced into the vagina from above at operation, together with placing two sponges in the cul-de-sac, and the maintaining of the vaginal cuff vertically on stretch, is sufficient to prevent any spilling of vaginal secretions intraperitoneally, as evidenced by lack of postoperative peritonitis.

Summary and Conclusions

1. One hundred and thirty cases of panhysterectomy are reported without preoperative vaginal sterilization.
2. A surgical technique is described to safeguard the peritoneal cavity from contamination.
3. There was no peritonitis or other complication which could be attributed to this technique.
4. A surgeon can therefore proceed with impunity in an unforeseen panhysterectomy, even though he has not prepared the vagina, provided the above-described technique is followed.

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CESAREAN SECTION ON A POLIOMYELITIC PATIENT CONFINED TO A RESPIRATOR

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PREGNANCY complicated by acute anterior poliomyelitis with paralysis of the respiratory muscles requiring continuous confinement in a respirator is rare. The number of patients in this group who have respiratory paralysis at term is small because so fulminating a process leads rapidly to death or to improvement before delivery. Aycock¹ reports that the incidence of pregnancy in all poliomyelitis cases is less than 1 in 1,000; and the incidence of poliomyelitis among pregnant women is less than 1 in 50,000. If Brahdy's² findings, that 4 per cent of all poliomyelitis patients are respirator cases, may be applied generally, then, hypothetically, less than 1 in 1,000,000 pregnant women would have respiratory poliomyelitis. Of these only a small percentage would still be dependent upon artificial respiration at the time of delivery. During the recent epidemic, in our experience with 423 cases of poliomyelitis, 40 of whom were women in the childbearing age, there were three pregnancies. The apparent discrepancy with Aycock's statistics may be attributed to the greater incidence in older age groups during this epidemic.

Peelen³ tabulates 29 reported cases of poliomyelitis in pregnancy, adding two of his own, and discusses various aspects of the problem. Gillespie⁴ reports a cesarean section in a pregnant woman with respiratory paralysis due to acute poliomyelitis. He unsuccessfully attempted to arrest labor with progesterone and large doses of nembutal, but finally performed a section to procure a live baby, as the mother was considered moribund. The mother improved, but the baby died six hours after birth of intracranial hemorrhage. Spishakoff, Golenternek, and Bower⁵ report a premature spontaneous delivery using a resuscitator alternating with the respirator. The mother's condition was so grave that they were prepared for a postmortem cesarean section. The insurmountable difficulty of forceps application and of low spinal or presacral anesthesia are discussed in their paper. Hornung and Creutzfeldt⁶ report a section performed three weeks before term upon a pregnant woman with respiratory paralysis. A respirator was not used, and she died forty-eight hours later of respiratory failure. The baby survived.

We disagree entirely with the belief, held by many, that poliomyelitis usually has no adverse influence on pregnancy, and vice versa. As is well known, bladder paralysis with cystitis and ascending infection may lead to pyelonephritis. Impaired bowel function, with constantly recurring fecal impactions and marked distention pressing on a paralyzed diaphragm, may increase the already serious hypoxia. Removal of a patient from a respirator to allow her to learn to breathe spontaneously for gradually increasing intervals is not without danger near term. Many authors have noted the disappearance of cyanosis and thoracic discomfort, and the onset of easier breathing upon emptying the uterus. McGoogan⁷ suggests that in some cases of poliomyelitis the added strain of pregnancy may retard complete recovery, but that after delivery, the burden having been removed, regeneration may progress more rapidly. In other instances, he believes, the disease might not have been so

extensive had pregnancy not been present. Poliomyelitis probably has no effect on the fetus in utero, as no authentic intrauterine infections have been reported. If any immunity is imparted to the baby during an attack in the mother, it must be short-lived, as a number of cases of infantile poliomyelitis have been reported under the age of 1 year, a few under 1 month, and one as early as 9 days.⁸

Cushny,⁹ in 1906, established the fact that the automatic rhythmic uterine contractions are on a myogenic, rather than a neurogenic basis, and that completion of the first stage of labor is possible after severance of all nerves to the uterus. Transection of the spinal cord, and even extirpation of the sympathetic nerve supply to the uterus, does not alter its inherent contractility. Obstetricians had observed previously that vaginal delivery is possible in women paralyzed by cord tumors and vertebral fractures, with loss of function of the muscles of the abdomen and extremities (Kleinberg and Horwitz¹⁰).

It is obvious that complete paralysis of all the voluntary forces definitely hinders the progress of the second stage of labor, and that in such cases external help is necessary. In addition, paralysis and overdistention of the bladder and bowel, with constantly reforming fecal impactions, necessitate frequent cathartics and enemas, which accentuate Braxton Hicks' contractions, thus possibly inducing labor prematurely. Bladder paralysis and distention may interfere with the normal third stage contractions and thus increase the possibility of hemorrhage (Miller¹¹).

Helms¹² believes that when respiratory paralysis is present during the last weeks of pregnancy, respiration will be facilitated by emptying the uterus, which he considers indicated. Morrow and Luria¹³ likewise suggest cesarean section if the increasing size of the uterus hampers respiration. McGoogan⁷ aptly states: "... emptying of the uterus should be done if the enlargement of the uterus is sufficient to encroach upon the diaphragm. This should be done . . . to improve the patient's lung aeration and to postpone the onset of fatal respiratory paralysis." Peelen³ is in accord with this view. Lewin¹⁴ says: "Interruption of pregnancy should not be undertaken except in those instances in which the uterus encroaches upon the diaphragm and there is diaphragmatic paralysis; or in case of severe cystitis or other complications." Brahdy and Lenarsky⁸ are of the opinion that "uncomplicated poliomyelitis, excluding respiratory paralysis, is not an indication for the interruption of pregnancy." In a personal communication from Kleinberg,¹⁰ he qualifies his published statement, saying that section may be indicated in a respirator patient.

There seems to be an erroneous belief that during the agonal period preceding death, the patient will have a precipitous delivery. This misconception may have resulted in a needlessly high rate of fetal mortality, which might have been avoided by more active measures. Fetal mortality in postmortem cesarean section is very high because futile attempts at maternal resuscitation are usually prolonged unduly.

In our case, the respiratory paralysis was accompanied by the loss of almost all voluntary motor function of spinal innervation, plus facial paralysis as a manifestation of bulbar involvement. The pregnancy was further complicated by breech presentation, pyelonephritis, and acute glomerulonephritis.

Case Report

E. M., a 27-year-old pregnant white housewife, was admitted to the Poliomyelitis Service of the Kingston Avenue Hospital on Aug. 26, 1944, with a two-day history of an ascending type of poliomyelitis; headache, vomiting, nuchal rigidity, weakness of both legs, fourteen-hour urinary retention, and then difficulty in breathing and weakness of the left arm.

Her history included one previous uncomplicated pregnancy which terminated five years ago in spontaneous delivery at term of a 7-pound, 13-ounce normal male child, after a labor of nine hours. An episiotomy was necessary. Her last menstrual period was March 15, 1944, and was normal. The pregnancy was uncomplicated prior to the onset of the present illness.

Examination on admission revealed an acutely ill woman whose voice was faint and skin dusky. She could count only to 2 in one breath. Her temperature was 101° F., pulse 100, and respirations 28. Her lungs were poorly ventilated. The abdomen was enlarged by a five-months' pregnancy and a markedly distended bladder. There was rigidity of the neck and back, and bilateral weakness of the iliopsoas, ham-strings, triceps, biceps, intercostals, diaphragm, and of the left deltoid. There was also slight left lower facial palsy. Deep tendon and abdominal reflexes were absent. The Kernig sign was positive bilaterally. Other findings were noncontributory. The spinal fluid was under increased pressure, slightly cloudy, sterile, and contained 520 cells per cubic millimeter, 70 per cent lymphocytes and 30 per cent polynuclears. Glucose was 66 and total protein 90 mg. per cent.

Upon admission, the patient was placed in a respirator. Her temperature became normal on the second hospital day, and it was then noted that the patient had no visible respiratory excursion when removed from the respirator, and turned cyanotic in a few seconds. Paralysis had extended to the right upper limb. Bearing down, coughing, and defecation were impossible. There was marked muscular pain in the extremities, chest, and shoulders, intensified by passive motion and pressure, as well as severe lower lumbar and right sacroiliac pain.

Painful intermittent uterine contractions appeared and became progressively more frequent and severe. They were often provoked by the cleansing enemas, which were necessary every other day despite the use of large doses of bland cathartics, oil enemas, and frequent digital removal of fecal impactions. External pelvic measurements were ample. Active fetal movements were present until delivery, but auscultation of the fetal heart was impossible because of the noise of the respirator. Frequent catheterization was necessary until the ninth day, when she developed paradoxical incontinence with a residual of 450 c.c. The urine specimens showed a trace of albumin and rare red and white blood cells. Culture was positive for *B. coli*. Mereurochrome was instilled into the bladder every second day in the hope of preventing ascending infection.

On the twentieth day, she developed acute right-sided pyelitis with large amounts of *B. coli* in the urine. On the sixty-eighth day, a superimposed acute diffuse glomerulonephritis appeared, and became progressively worse.

At no time was edema evident. On the seventy-seventh day the patient vomited persistently for twenty-four hours, returning food eaten more than twelve hours previously. She had almost continuous uterine contractions during that day. Vaginal examination revealed a thick, long, closed cervix. The patient had been confined to a respirator continuously for ten weeks, and as the pregnancy advanced both the rate and pressure had to be increased to compensate for the greater resistance to diaphragmatic motion.

Considering the nephropathy and the fact that the fetus was in breech presentation, it was deemed advisable to take advantage of a slight improvement in the patient's general condition to do a cesarean section at the thirty-fifth week of gestation, eighty-two days after admission. Consultations confirmed our decision, lest by delay we permit further kidney damage and perhaps intrauterine fetal death. A third transfusion of 500 c.c. of whole blood was given. Because the respirator could not be moved to the main operating room, an emergency operating room was improvised. An endotracheal tube was passed. The patient was removed from the respirator and maintained with a resuscitator until anesthesia was begun. Under cyclopropane insufflation anesthesia, with manual positive pressure to a re-breathing bag, a classical cesarean section through the placental site was done. A healthy 4-pound, 5-ounce premature female child was extracted by the breech in three and a half minutes, crying and breathing spontaneously. Placenta and membranes were removed manually. The uterus contracted well after pituitrin and was closed in layers. The abdomen was closed by our usual technique.

The entire time from incision to closure was twenty-five minutes. When the operation was completed, the Kreiselman apparatus was again used until the patient was returned to the respirator. The sutures were cut on the seventh postoperative day and removed on the ninth, with healing per primam.

The baby was given routine neonatal care and was transferred to a premature unit at the Kings County Hospital. Her course was uncomplicated and, at four months, she weighed 9 pounds.

The facilitation of chest expansion detected by the anesthetist upon removal of the baby was noted by the patient as she recovered from the anesthesia, and she was more comfortable thereafter, even at a reduced respirator pressure. The patient voided spontaneously five hours after the operation. Her oral temperature rose to 100.4° F. eleven hours postoperatively, but subsided promptly. Gaseous distention was absent throughout. Prostigmine and a rectal tube were employed prophylactically.

The breasts continued to secrete in spite of early and prolonged use of stilbestrol, supplemented later by testosterone. The patient could not tolerate a breast binder because it restricted the full chest expansion produced by the respirator.

Both forearms have a limited range of feeble motion, and the hands can be used effectively. The lower limbs can manifest feeble mass movements. The slight left facial paralysis remains unchanged.

The blood chemistries and the urine returned to normal within a month after the operation, except that urine cultures are still positive. In spite of 500,000 units of penicillin, a prolonged course of sulfadiazine, and the protracted use of ammonium mandelate and ammonium chloride, the urine has not been sterilized. The red blood count has risen to 4,350,000 and the hemoglobin 81 per cent. The blood pressure has fallen and varies between 110/60 and 140/100.

Comment.—The care of a patient confined to a respirator is limited by the difficulty of manipulation. Since the patient was entirely dependent upon the respirator, we were cautious not to remove her from the apparatus for more than two minutes at a time, to avoid fetal anoxia. Only after delivery was any attempt made to determine how long the patient could remain out of the respirator.

The generalized muscular pains due to the extensive poliomyelitic involvement and the costovertebral pain associated with the kidney infection, prevented change of position and other manipulation. The gravid uterus contributed to the respiratory embarrassment and to the ascending urinary infection. The patient was constantly wet because of urinary incontinence and perspiration, aggravated by the summer heat. One of us (S. S. B.), in order to reduce the humidity of the air within the respirator and thus facilitate the evaporation of perspiration, introduced anhydrous calcium chloride as a desiccating agent. We feel that this contributed greatly to the patient's comfort and minimized moisture as a factor in the formation of bedsores. Pressure and stasis could not be relieved because passive motion produced most agonizing pain.

On admission, as the prognosis was doubtful, provision was made for post-mortem cesarean section. However, the patient's condition remained static and the problem of ultimate delivery confronted us. Consultation with specialists in obstetrics and anesthesiology suggested the following methods of delivery: (1) spontaneous delivery, (2) delivery after full dilatation of the cervix assisted by low forceps or pituitrin, (3) abdominal cesarean section, classical or low double flap.

Vaginal delivery within the respirator is possible, but offers little opportunity for control and asepsis because of the size of the chamber and the spacing of its portholes.

The respirator^{15, 16} consists of a huge airtight cylindrical chamber enclosing the patient's body with the head protruding through a rubber collar. A bellows or a diaphragm operated by an electric motor produces rhythmic changes of pressure. The chamber has several portholes. Breech extraction, forceps to the aftercoming head, episiotomy, manual removal of the placenta, repair of a lacerated cervix or perineum, and control of postpartum hemorrhage are impossible. Delivery within a respirator is further contraindicated by the danger to which a newborn infant is subjected, being unable to synchronize with a respirator set at an adult rate and pressure. Moreover, the changes in atmospheric pressure within the respirator, equivalent to sudden ascent and descent from an altitude of about 1,300 feet, might cause pulmonary or intracranial hemorrhage or air embolism. Other means of artificial respiration during labor might have overcome some of these objections and permitted vaginal delivery. However, the fetus being in a breech presentation, and faced with the threat of prematurity, the pressure of uterine contractions on its head would not be insignificant. A possibly rapid extraction through an unprepared genital passage would be hazardous. We also felt that a patient unable to cough, defecate, or breathe because of broken reflex arcs, is sufficiently handicapped to be spared the added strain of labor.

The classical section was selected as the fastest and simplest method, and the various means of anesthesia and resuscitation at our disposal were then studied. The anesthetic aspect is discussed at length in a companion paper.¹⁷ Cyclopropane was chosen as the safest and most flexible agent, allowing one anesthetist to control both aeration and anesthesia.

An experimental head respirator designed by J. H. Emerson for use in this case was abandoned because it precluded the use of inhalation anesthesia. The chest respirator could not be used because of the time required to apply it even to a normal, cooperative subject, and because it would have interfered with abdominal surgery. The plan to build a special respirator room similar to the one in Boston was given up after consultation with naval experts because the effect of the constantly changing pressure was feared.

Positive pressure, using a face mask, at first with a rebreathing bag and later with the Kreiselman¹⁸ resuscitator, was employed frequently both to accustom the patient to its use and to facilitate examination, treatment, and nursing care. Manual compression of the rubber bag distends the lungs, and when properly performed provides good aeration at no hazard. An automatic modification, the E & J resuscitator, caused discomfort and apprehension in our patient. Gaseous anesthesia cannot be given with this machine, nor with the Kreiselman resuscitator, which furnishes oxygen through a face mask at an adjustable pressure that is both safe and adequate. The rate and rhythm are under the control of the operator, and can be made to supplement any voluntary respiratory efforts of the patient, while most other devices may oppose them. Our patient did well on the rebreathing bag, but fatigue of the operator led to irregularities in the rhythm and depth, which in turn made the patient fearful

and uncooperative. She was, on the other hand, relaxed and confident when the Kreiselman apparatus was used, and had smooth and even oxygenation at all times. She was therefore maintained with this resuscitator in transit between the respirator and the operating table, and until anesthesia was begun. Fully satisfactory anesthesia was given under positive pressure from the rebreathing bag, after passage of an endotracheal catheter under direct visualization. The new Kreiselman bellows¹⁹ resuscitator, which is manually operated and can deliver gaseous anesthesia and oxygen, was an alternative means.

We believe that the action of the respirator played a large part in preventing distention, whether by a milking action or by preventing splinting of the abdomen, and helped prevent pulmonary complications by forcing full chest expansion. Though we had feared that delayed healing would follow from the constant abdominal motion caused by the respirator, we were favorably surprised. Prolonged uncontrollable lactation was the only possible untoward effect of the respirator, which simulated a large breast pump.

Summary and Conclusions

A case of pregnancy complicated by acute anterior poliomyelitis appearing in the fifth month and necessitating the continuous use of a respirator has been presented.

We believe that a patient with a quadriplegia plus almost total paralysis of all the muscles below the clavicles should be spared the added strain of labor. The pregnancy was further complicated by acute pyelonephritis and acute diffuse glomerulonephritis. The progression of this nephropathy and the possibility of intrauterine fetal death required prompt action.

The patient was removed from the respirator and maintained with positive pressure resuscitation and insufflation anesthesia with cyclopropane, while a classical cesarean section was performed. A healthy premature baby was delivered at the thirty-fifth week of gestation, followed by improvement in the condition of the mother. The subsequent course of events confirms our decision that an elective cesarean section was the best procedure under the circumstances.

The rationale of treatment is given, with discussion of means of anesthesia and resuscitation. The use of anhydrous calcium chloride is recommended to increase the comfort of respirator patients. The method presented is believed by us applicable to all respirator cases requiring laparotomy.

Addendum

Follow-up.—The authors regret to report that the patient succumbed on July 14, 1945. Her urinary infection persisted and, five months post partum, stones were first observed. Subsequently, a left perinephritic abscess developed which required incision and drainage. Three months postpartum, the patient developed a massive atelectasis with almost complete shifting of the heart and mediastinum into the right chest. Bronchoscopic suction gave only temporary relief. These complications resulted in the patient's death 322 days after admission and 242 days after laparotomy.

We are greatly indebted to Drs. E. A. Rovenstine of New York City and Joseph Kreiselman of Washington, D. C., for the able handling of the anesthesia, without which we could not have succeeded. We also thank Drs. A. C. Beck, Harvey B. Matthews, and Morris Glass of the Long Island College of Medicine and Dr. H. J. Stander of the Cornell University College of Medicine for their consultation, and Dr. Nathan Reibstein for his technical assistance, as well as our many other colleagues who advised us by mail. We are grateful, too, to Dr. E. M. Bernecker, Commissioner of Hospitals, who placed all necessary facilities at our disposal, without which this mother and baby could not have survived.

755 OCEAN AVENUE

1045 ST. JOHNS PLACE

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DOUBLE UTERUS AND DOUBLE VAGINA

Identical Doubles Demonstrated by Colpohysterosalpingography

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TAYLOR¹ wisely advocated simplification and uniformity of nomenclature relating to organic variants which are the result of lack of fusion of the Müllerian ducts and/or irregularities of canalization. With his position we are heartily in accord. This author cited DeLee as listing nine variations and Graves eight types which do not correspond. He further declared that the many terms do not give a word picture, but require a detailed description. His simplified classification follows:

1. Uterus arcuatus.
2. Double uterus with a single cervix.
3. Septate uterus with a single or a septate vagina.
4. Double uterus with a double cervix.
5. Uterus with a rudimentary horn or absence of one horn.

It is not our intention to discuss extensively here these embryologic phenomena, but simply to reiterate the well-known fact that these variants from normal are due to irregularities of fusion in the juncture of the Müllerian ducts, which normally form the symmetrical halves of the corpus uteri. These abnormalities may also be associated with irregularities in canalization in the development of the urogenital sinus or lower uterine and vaginal tract.

Frequency of Occurrence

As estimated by Taylor,¹ the deformity occurs once in about 1,500 obstetric cases and once in about 2,000 gynecologic cases. He thought that even the specialist may see but a few cases in a lifetime. Ewer² was of the opinion that abnormalities of the female generative tract are more frequent than one is prone to believe, and cited Falls, who noted the presence of uterus arcuatus in 3.8 per cent of 7,553 obstetric cases. Moore³ also believed the incidence of this abnormality is much higher than the imperfect records would indicate and from private records drew the conclusion that "one in five or six hundred women present some definite congenital deflexion from gestation slips in the embryological assembly line." He also thought many women go through life without awareness of the abnormality or at least without disclosing the condition. This author further observed that this anomaly is frequently associated with abnormalities of the genitourinary system and mentioned several cases on record in which pregnancy of both uteri occurred concurrently with safe outcome to both babies and the mother. Conversely, Obenour,⁴ in 1942, searched the literature published since 1879, but could find no record of roentgenograms or of actual photographs of double uterus and vagina.

Practical Considerations

Schauffler⁵ quoted the record of a case which included the more incorrect than correct diagnoses made by nine physicians, and also this comment regarding the patient, "She was unnecessarily pounded, thumped, curetted, aborted, and laparotomized, mainly because of a complete double uterus which presented diagnostic difficulties during pregnancy." He also observed that this functional variant is a definite asset to marital relations and inferred that fertility and the sex urge are distributed among women with this abnormality in the same generous proportions as their organic equipment. He reported seeing eleven patients in six years with duplex anomalies of the urogenital tract. Each had one or more pregnancies, and there was a total of thirty-two.

Ewer² cited Findley, who in 1926 analyzed 135 cases of uterus didelphys with septate vagina reported in the literature. The patients in these cases gave birth to 216 full-term babies, including 13 sets of twins; 83 were delivered spontaneously, and 23 by cesarean section; 13 presented by breech. Fifteen were born prematurely, and there were 86 abortions. This author then sagely observed that Nature is resourceful and noted the corollary seen in many mammals thus normally equipped. He added that if this is only an expression of atavism, "it is perhaps surprising that trouble is not more often encountered."

Diagnosis

Helpful diagnostic signs in this condition are, according to Schauffler,⁵ "irregular menses, dyspareunia, repeated unexplained abortions or miscarriage, and repeated malposition of fetus." Uterosalphingograms, he stated, yield the most complete information available. All writers agree that pseudomenstruation from the nonpregnant side occurs commonly and may be a sign of threatened abortion because the decidua is under a different endocrine influence. Passage of a decidual cast should always be investigated, though it is not necessarily indicative of threatened abortion. Schauffler⁵ advised general and special prenatal care, and measures to strengthen and protect the ovular attachment.

There is general agreement that the nonpregnant horn rotating posteriorly and altering the birth canal is a common complication. Awareness of this anomaly at delivery calls for ready operative equipment for complications involving the vagina and cervix. Taylor¹ declared that "incarceration of the nonpregnant uterus with a breech presentation at term is an absolute indication for delivery by cesarean section." Post partum, likewise, there may be adherent placenta, postpartum hemorrhage, faulty involution, and other irregularities. We believe that roentgen pelvimetry should be added routinely to the armamentarium of the diagnostician.

Report of Case

Mrs. C. E. B., a white woman aged 24 years, first came under our observation on Sept. 10, 1944. The reason for consulting a physician at this time was nervousness, pain in the lower part of the abdomen aggravated by intercourse, irregular menses, and severe cramps with menses, causing her to remain in bed for from one to three days during each menstrual

period. Sterility was also a prominent complaint. Although she had in the past years consulted ten physicians, none had ever advised her of her abnormal condition.

She had had the usual diseases of childhood. Menses had begun at the age of 15 years and had always been irregular and painful. First married at the age of 18 years, she had after eleven months been divorced. She had been married since she was 22 years of age to her present husband. She had never experienced any sense of gratification in the sexual act and had never been pregnant. Following an acute attack of appendicitis five years previously, an appendectomy had been performed. There was no history of venereal disease.

The patient was 66 inches in height and weighed 158 pounds. The blood pressure, taken on several consecutive occasions, averaged 125/75. Urinalysis of a catheterized specimen gave negative results. On two occasions the reaction to the Kahn test was negative.



Fig. 1.—Following injection of iodochlorol into the cervixes through a catheter, two cervixes, two cervical canals, two separate uteri, and two tubes are clearly outlined in this roentgenogram. The tube on the right side is partially filled with oil and air; the tube on the left side is well filled with the opaque oil.

On examination of the genital tract, it was noted that a complete septum was present in the vagina extending down to within $\frac{1}{2}$ inch of the external orifice. Two distinct cervixes were palpated, with the septum extending in the vagina up to and forming a complete vaginal wall to the separate cervixes.

The patient returned for examination at the first menstrual period, which began three days after the first visit. The menstrual flow was demonstrated coming equally from the separate cervixes.

The roentgenologic report from here on proved most conclusive. A small catheter was introduced into the uterine canal on each side and injected with about 5 c.c. of iodochlorol. As shown in Fig. 1, the roentgenogram then taken plainly demonstrates only one tube to each of the separate uteri. These tubes are patulous and appear normal. The two cervixes, two

cervical canals, and two separate uteri are also clearly outlined. Roentgen study of the urinary tract showed, on intravenous injection of neo-iopax, no evidence of reduplication of the kidneys or ureters. In addition, roentgen examination of the chest gave entirely negative results, and the results of roentgen pelvimetry were also normal.

Summary

Simple and uniform nomenclature for describing abnormalities of the female genital tract is advocated. It is suggested that these anomalies occur more frequently than is generally believed. Diagnostic signs are reviewed, and routine roentgen pelvimetry as an aid in diagnosis is advised.

A case is reported in which a double uterus and a double vagina were demonstrated roentgenologically.

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THE SUBPERITONEAL BALDY-WEBSTER UTERINE SUSPENSION*

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SINCE Olshausen performed the first modern suspension of the uterus, many techniques have been devised, practiced, and discarded. Because of the principles embodied in the Baldy-Webster type of uterine suspension, this procedure has been able to enjoy wide popularity and use among gynecologists for many years. The utilization of the proximal end of the round ligament to support and elevate the prolapsed ovary, together with the fact that the uterus remains a mobile pelvic viscus not attached in any way to the abdominal wall, are the main factors responsible for the success of the operation. It has been demonstrated repeatedly that this procedure causes no complication in subsequent pregnancy and holds up well following delivery.

There are, however, several points of weakness in the procedure. The first disadvantage is the necessity of perforating the broad ligament in order to draw a loop of the round ligament through it. This has resulted in intestinal obstruction. Since Richardson² reported the first such complication, following the Baldy-Webster procedure in 1920, ten other cases have been added to the English literature.³⁻⁹ This serious complication, sometimes developing years after the performance of the operation, was due in every case to the incarceration of a knuckle of bowel into the opening in the broad ligament which had become enlarged by the traction of the uterus during the years.

The second disadvantage lies in the presence of the joined and uncovered loops of round ligament on the posterior surface of the uterus. This area with its knots of suture material offers a congenial site for the development of intestinal adhesions with their many potential sequelae. Such a case was observed in which the bowel was adhered to this area on the back of the uterus causing partial intestinal obstruction and necessitating a second laparotomy two weeks after the first. Another disadvantage is the possibility of failure of the suspension because of the lack of union between the serosa of the round ligament and the serosa of the uterus at the small area of suture contact between the two.

With the idea of avoiding these disadvantages, one of us (E. A. S.) in 1942, devised a subperitoneal approach which accomplished the identical results of the Baldy-Webster procedure without its drawbacks. The operation is performed as follows:

Method

After anesthesia and proper preparation, the lower abdomen is incised in the midline as for any intrapelvic procedure. The retroverted uterus is elevated and held in ante-position. A vertical incision, $\frac{3}{4}$ to 1 inch long, is made on the posterior uterine wall, its upper end corresponding to the intertubal line (Fig. 1). This incision is very superficial, only the peritoneal covering of the uterus being divided.

*Presented at a meeting of the Philadelphia Obstetrical Society, Feb. 1, 1945.

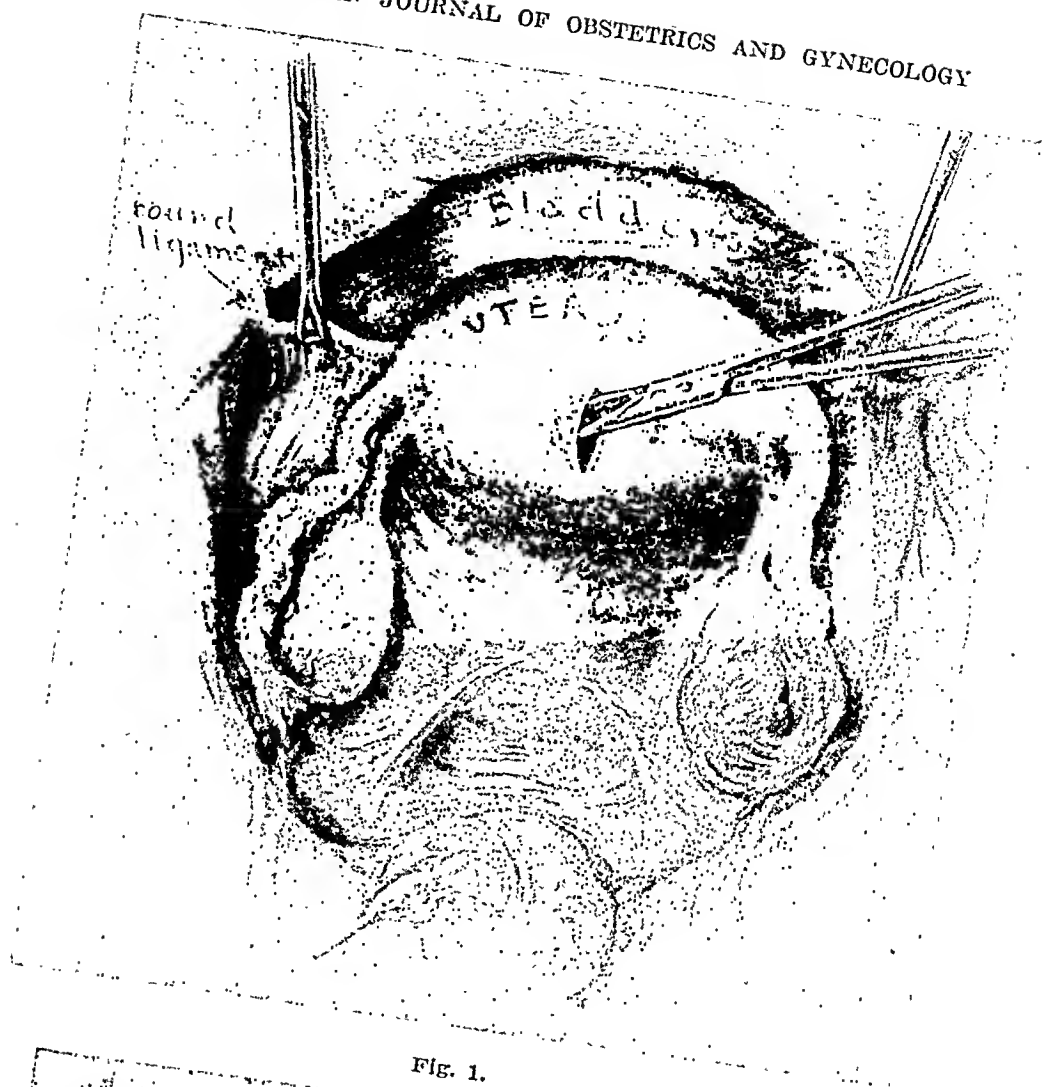
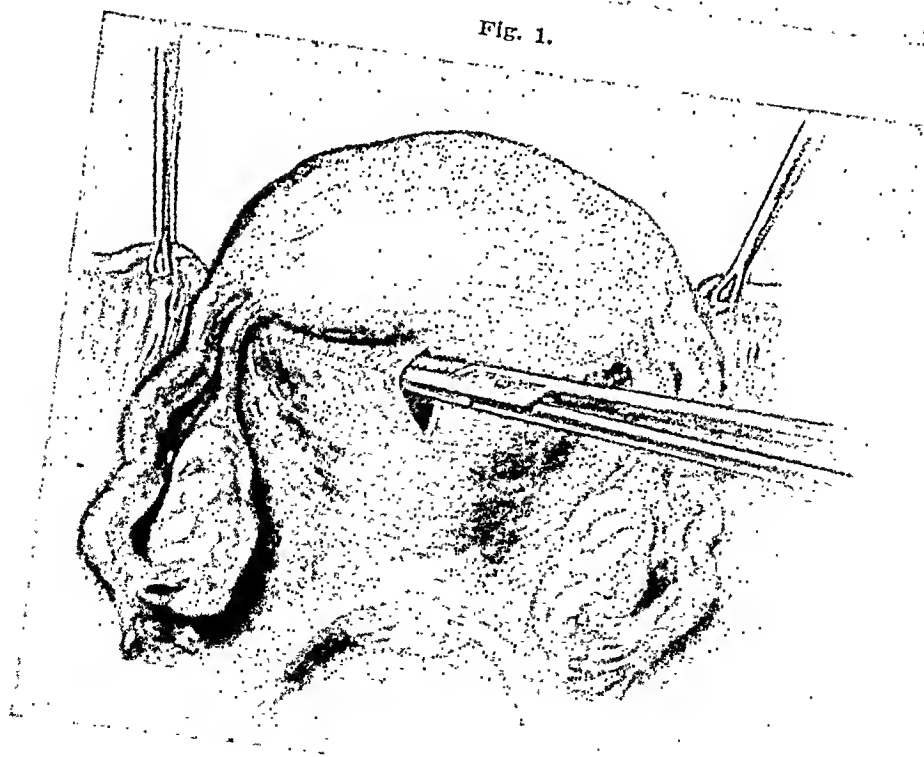


FIG. 1.



With a slender pair of Mayo scissors, a subperitoneal tunnel is made in the posterior uterine wall extending to the insertion of the broad ligament on either side. A slender long-nosed curved hemostat is then introduced into the tunnels on either side and the anterior leaflet of the broad ligament is pierced (Fig. 2). The round ligament is then grasped in the hemostat at the point of its greatest mobility and the loop of ligament drawn back through the tunnel until it appears at the uterine incision (Fig. 3, *A*). This being accomplished on both sides, the loops are approximated with one or two sutures of fine silk, linen or catgut depending upon the preference of the surgeon (Fig. 3, *B*). The vertical incision in the uterine peritoneum is then meticulously closed with very fine catgut and the operation is complete (Fig. 3, *C*).

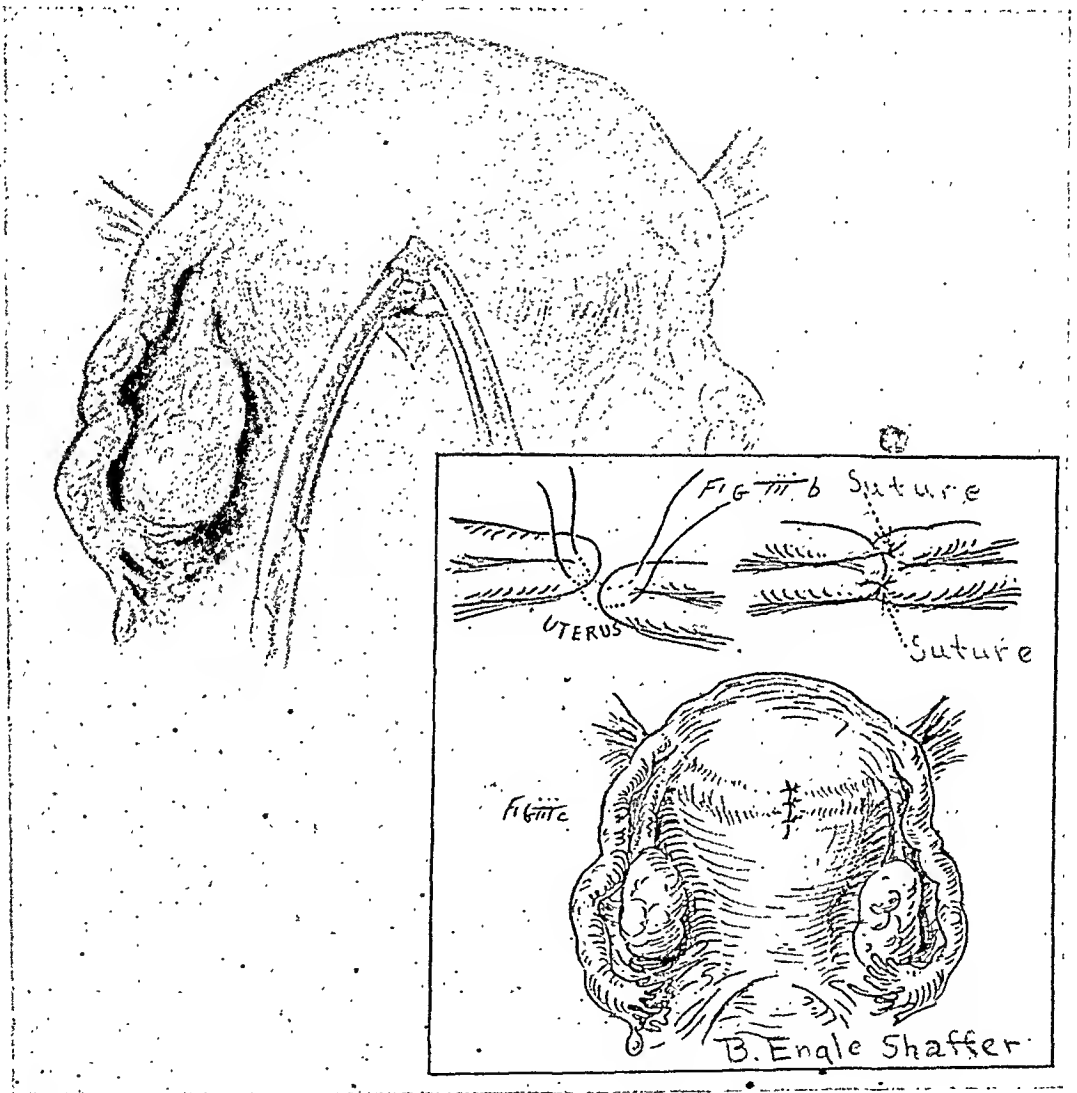


Fig. 3.

It will be noted that the posterior leaflet of the broad ligament is not perforated, so that no opening exists through which the bowel might herniate, nor are there the exposed loops of round ligament on the posterior surface of the uterus. There is much less chance of the suspension breaking down because agglutination between the uterus and round ligaments takes place in two long, buried, and scarified tunnels.

The mechanical principles involved in the original Baldy-Webster operation have not been modified in any way. The uterosacral ligaments may be sutured together when they are greatly relaxed. We have not found it necessary to advance the bladder as proposed by Curtis.

After this method had been practiced for about a year, a search of the literature disclosed the fact that Lagerson¹⁰ of Minneapolis had reported an almost exactly similar operation in 1931. However, Lagerson's paper did not excite much attention and was wholly unknown to us. Because of this and the fact that the gynecologists over the country are not familiar with this valuable technique, we have been prompted to give this report, it being understood that priority for the operation clearly belongs to Lagerson.

There have been thirty-two cases in which the above plan has been followed, with no complications up to this time, and with no known disadvantages. In all of them the anatomic result has been excellent, and the relief of the symptoms complained of satisfactory.

Operations for retroversion of the uterus, too often performed upon flimsy indications a few years ago, have fallen into an unfortunate degree of unpopularity. It is now quite fashionable to decry any surgical attack upon retroversion, which is regarded by some as a nonsurgical condition not responsible for any real disability on the part of the patient.

Theilhaber¹¹ many years ago first called attention to the fact that uncomplicated retroversion may occur without symptoms. It is well known that congenital retroversion, which is far from being uncommon, seldom causes symptoms. It is also true that the normal position of the uterus in elderly women is that of partial retroversion, and that some of the secondary retrodisplacements in young women, especially after childbirth, cause no symptoms.

It is our experience, however, as well as that of others,¹² that symptoms often postdate the secondary development of retroversion, as the unnatural position causes an impediment to the return circulation with resultant engorgement of the uterus and adnexae. These symptoms are most often sacral backache, menstrual disturbances, and fatigue. This condition is a menace to the health of the ovaries and is responsible for the large, pale, edematous ovaries which function abnormally. Retroversion is often a precursor to prolapse of the uterus¹³ and is commonly associated with other pelvic pathology; in Gardner's¹⁴ cases, 94 per cent had other pelvic pathology. Endometriosis is almost always accompanied by backward displacement of the uterus, and sterility is not uncommon.

The gynecologist, therefore, when treating retroversion of the uterus, assumes a responsibility which demands most careful differentiation between cases. All other pathology should be ruled out before considering surgery. In the clinic at the Kensington Hospital for Women, such patients are treated by the insertion of a Smith or Smith-Hodge pessary. If symptoms are relieved for three months, the pessary is withdrawn. In a definite proportion of patients the tone of the supporting structure has been restored, the organ remains in normal anteversion, and the disability disappears. In other patients the uterus shortly becomes retroverted again and the symptoms recur. It is in this group that permanent support seems indicated and in which a surgical suspension brings relief.

Conclusions

1. The Baldy-Webster suspension operation is discussed as to its advantages and disadvantages.

2. The subperitoneal approach is described which avoids the weaknesses of the old Baldy-Webster technique.

3. Retrodisplacement of the uterus is discussed as to symptomatology, cause, and treatment.

1814 SPRUCE STREET

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APLASTIC ANEMIA SIMULATING ECTOPIC GESTATION

Report of a Case

S. KOLODNY, M.D., AND S. T. DELEE, M.D., CHICAGO, ILL.

(From the Obstetrical Department of Cook County Hospital)

ECTOPIC gestation is said to occur once in 200 pregnancies.¹ It is one of the most frequently misdiagnosed acute surgical conditions of the abdomen, so that even in good hands one in four cases is missed. The chief reasons are the atypical history and inconsistent findings. Hence, ectopic pregnancy is justly called the "lues of the abdomen."

It is not the purpose of this report to discuss the differential diagnosis of ectopic pregnancy; however, in reviews of this subject, aplastic anemia is not mentioned nor were we able to discover in the literature a case similar to ours. That this report may have added significance and also by way of interest, a brief discussion of aplastic anemia is presented.

Aplastic anemia was first reported by Ehrlich in 1888.² In 1919, Smith³ reported 64 cases. Its etiology is unknown; however, an unidentified toxin is believed to act upon bone marrow, impeding its activity and causing atrophy. Certain chemical and physical agents have been mentioned, namely, benzol, coal-tar derivatives, gold salts, as well as salts of many metals such as arsenic. Mustard gas, x-rays, and radium have also been suggested. Following septic conditions, such as typhoid and diphtheria, patients have developed aplastic anemia. Parasitic infections, such as ankylostoma, may be a factor. In terminal cases of pernicious anemia and hemolytic anemia, the bone marrow may present the picture of aplastic anemia. Lescher and Hubble⁴ believe the disease occurs more often in females, especially between the ages of 15 to 30 years; however, in Thompson, Richter, and Edsall's⁵ report of thirteen cases, twelve occurred in males. The youngest patient was 25, the oldest 70, and the average age was 46 years. There is no suggestion of a familial tendency.

The onset is usually insidious, with weakness and a progressive pallor. There may be petechiae or purpuric manifestations. Hemorrhages may occur in the skin, mucous membranes, or any organ of the body, but this is usually a late manifestation. Fever is frequently present. Usually there is no undue loss of weight. On physical examination, there is extreme pallor of the skin, without a lemon-yellow tinge. The heart may be dilated and there may be a systolic murmur on the basis of an anemia. The liver, spleen, and lymph nodes may or may not be enlarged.

The blood picture usually shows erythrocytes 1,000,000 to 1,500,000, hemoglobin about 20 per cent, color index less than one, a leucopenia with about 1,500 leucocytes, platelets usually below 50,000, and an accelerated sedimentation rate. Bleeding time is usually not increased, but clotting time is delayed and there is poor retraction of the clot. The reticulocytes are slightly to moderately increased, with a reduction in the neutrophils. Normoblasts are present. The granulocytes show a definite shift to the left. The red cells on blood smears are varied in size and shape, but there is no definite macro- or microcytosis. Poikilocytosis, anisocytosis, and polychromasia are absent. Hurwitt,⁶ in a report of the subject, recorded 30 cases, 14 of which occurred during pregnancy. He concluded that the pregnancy may not have been coincidental, but that it may have played an etiological conditioning role.

Case Report

A 29-year-old white woman, gravida ii, para i, was admitted to the Cook County Hospital on May 31, 1944, with the history that at 8:00 A.M. she awoke feeling weak and dizzy, went to the bathroom and fainted. When she recovered she had severe epigastric pain.

Her last menstrual period occurred on May 20, 1944; it was very profuse and lasted seven days. Ordinarily her periods were every twenty-eight to thirty days and of five days' duration. Her occupation was that of a factory radio worker, in which she ground quartz crystals using carbon tetrachloride. In the previous ten days she had noticed that her gums bled easily.

The physical examination revealed a very anemic patient who appeared acutely ill. The blood pressure was 114/46, temperature 100.6° F., pulse 100, and respirations 24. On auscultation a soft systolic apical murmur was heard. On her back were several small areas of ecchymosis. On abdominal palpation, there was tenderness in both lower quadrants. Pelvic examination revealed tenderness in both adnexal areas with bulging into the cul-de-sac. The cervix and uterus were normal. The blood examination showed 690,000 erythrocytes, 2,200 leucocytes, 35 per cent hemoglobin, and a color index of 0.4.

The impression was ruptured ectopic pregnancy; a blood dyscrasia was considered. When 20 c.c. of blood were easily obtained by colpocenteses of the posterior cul-de-sac, the former diagnosis was supported and a laparotomy was done, the patient first receiving blood and plasma. The pelvis was full of fresh dark blood, the uterus, tubes, and ovaries were normal except for bleeding from the ostium of the left tube, which on stained section later proved to be normal microscopically. A left salpingectomy was done, the idea of a tubal abortion being entertained.

Following surgery another transfusion was administered and for three days the patient's condition steadily improved and was satisfactory. On the fourth day she became somewhat icteric and developed petechiae of the forearms, gums, and conjunctivae. A blood dyscrasia was again considered and a hematologist consulted. At this time the erythrocytes were 2,240,000, leucocytes 2,200, hemoglobin 23 per cent, platelets 125,000, icteric index 40, cevitic acid level 35, nonprotein nitrogen 29, uric acid 3, and chlorides 580. The blood cultures were negative. The fundoscopic examination showed a hemorrhagic retinitis. A sternal puncture done on June 8 gave the following findings: "Marrow for the most part fibrotic with an incomplete disappearance of normal cellular elements. These cells do not appear young. Throughout the marrow one finds an occasional group of what appear to be diplococci. The opinion is that the material represents an aplastic marrow with secondary lymphoid degeneration as evidenced by the maturity of the cells seen." Thus a diagnosis of aplastic anemia was made.

In spite of repeated transfusions, vitamins C and K, iron and liver, the patient ran a downhill course and on the nineteenth postoperative day, when her temperature went to 106° F., she expired. An autopsy was performed and the following findings reported: hemorrhagic diathesis; petechial hemorrhages of all serous surfaces, skin and conjunctiva; hemorrhage into the right auricle and auricular appendages, edema of lungs; diffuse bronchopneumonia of both lungs; extreme gas formation in all organs, especially liver and spleen (a direct smear from the peritoneal cavity showed *B. welchii*—order of same present); hemorrhagic gastritis, hematometrium with blood coming from right tube; free blood in pelvis.

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HYDATIDIFORM DEGENERATION OF PLACENTA, COMPLETE WITH FETUS

ABE CLINE, COMMANDER, MC, USNR, JACKSONVILLE, FLA.

MRS. L. R., 18-year-old white married woman, was admitted to the Navy Dependent Hospital on Feb. 26, 1945, complaining of cramps and vaginal bleeding. Her last normal menstruation began in September, 1944. Irregular bleeding started two weeks before admission and continued intermittently until Feb. 25, 1945, when it became continuous and more profuse. She had experienced cramplike pains for several hours.

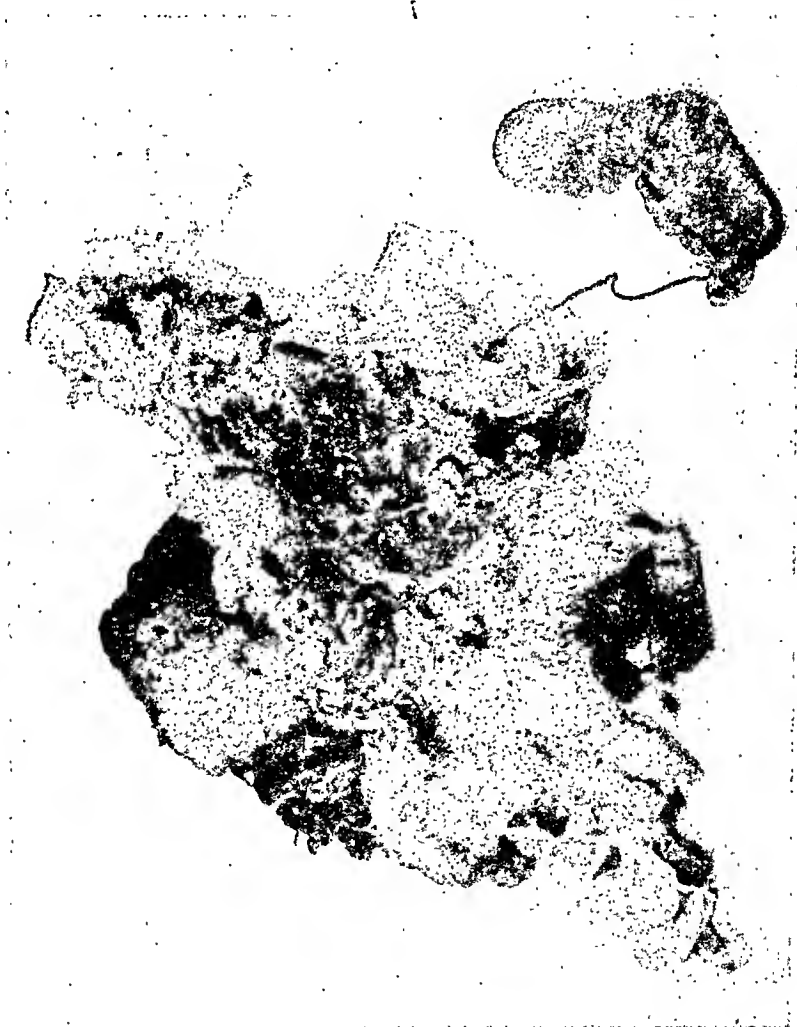


FIG. 1.

On admission, vaginal bleeding was moderately profuse. Ergotrate, 1/320 grain, was ordered three times a day, and codeine with aspirin for pain. Later, on examination, a dark red, firm, clotlike mass presented just within the vulvar orifice. It was removed with a sponge forceps. Grossly, the mass seemed to be placental tissue and was sent to the pathologic laboratory. The pathologist reported finding hydatid vesicles, whereupon I performed a curettage. A moderate amount of endometrium and clots were obtained.

More careful inspection of the original specimen showed that it included a small, papyraceous fetus within a sac, attached by an umbilical cord to a placenta which had undergone partial hydatidiform degeneration. The complete pathologic report by Lt. Comdr. Carl L. Minier follows:

Macroscopic Report.—Placenta measuring approximately 10 cm. in diameter is studded with numerous pedunculated cystic structures ranging from 2 mm. to 1 cm. in diameter. The amniotic sac which is attached contains a tiny, macerated fetus, "folded," and approximately 4 cm. in length, deep brown in color, which is attached by an umbilical cord 8 cm. in length, and less than 1 mm. in diameter.

Microscopic Report.—The placental villi are markedly enlarged and markedly edematous. There is considerable hyperplasia of the syncytium, the cells of which are enlarged, pale-staining, and show considerable vacuolization of the cytoplasm. Many of the distended villi form what appear to be small cystic structures containing small amounts of fibrin and filled with clear fluid. There is no evidence of malignant change.

Diagnoses.—(1) Hydatidiform mole, (2) degenerated fetus, six to eight weeks.

The specimen is of interest in that it shows a fetus of six to eight weeks' size, with a placenta of about sixteen weeks' size.

The patient made a prompt recovery and has had very little bleeding since. Friedman tests have been negative to date, but she will remain under observation.

4715 CEDARWOOD ROAD

Department of Reviews and Abstracts

Review of New Books

Obstetrics and Gynecology

H. J. Stander's third revision of Williams' *Obstetrics*¹ constitutes the ninth edition of this classic American textbook, the first six of which were prepared by the late Dr. J. Whitridge Williams, the well-known professor of obstetrics at the Johns Hopkins University School of Medicine. The work has been given a new title, *Textbook of Obstetrics*, but continues to carry out the original significance as a book for students and practitioners. Many changes and additions have been made both in text and illustrations, among which attention may be drawn to the following:

The general organization has been revised and improved through the utilization of the newer and more popular plan of sections with subheadings. Considerable data have been added concerning the developmental anatomy, neurology, endocrine physiology, and development of the ovum. Teaching of the mechanisms of labor for the various presentations has been facilitated by the replacement and addition of several illustrations. The section on amnesia, analgesia, and anesthesia in labor has been extensively revised, including discussion of the newer drugs and techniques. The general subject of the complications of pregnancy has been rewritten and brought up to date, including the section on toxemias.

Some medical schools teach only clinical pelvimetry and clinical or etiological classifications of contracted pelves, while others limit their instruction to morphologic classifications based on x-ray pelvimetry, these topics have been presented in separate subsections, and each is fully discussed.

Additions have been made in the section devoted to operative procedures and new illustrations have been added. Finally, the subjects of puerperal infection and diseases of the puerperium have been revised to include the newer methods of therapy.

This excellent presentation, devoted to an important and major branch of medicine, is well worthy of the attention which has been extended to previous editions. It remains the classic volume in American textbook literature on the subject.

GEO. W. KOSMAK.

The Management of Obstetric Difficulties, by Dr. Titus,² offers an extensive discussion of the abnormal conditions which may develop during the reproductive process. The broad viewpoint held by the author is reflected in the inclusion of chapters on sterility, late complications of the puerperium, and accidents, birth injuries, and asphyxia of the newborn. There is much material in this revision on x-ray pelvimetry, which is well illustrated; and the toxemias of pregnancy, for which the author proposes a new classification. In the discussion of analgesia and anesthesia in labor, the technique of Hingson and Edwards has been included in detail. The method is not, however, placed on the list of the author's preferences

¹*Textbook of Obstetrics (Formerly Williams' Obstetrics)*. By Henriens J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College; Obstetrician and Gynecologist-in-chief, The New York Hospital; Director, New York Lying-In Hospital, New York City. D. Appleton-Century Co., New York. 1945.

²*The Management of Obstetric Difficulties*. By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh. Third Edition, 376 pages, 426 illustrations and 8 color plates. The C. V. Mosby Company, St. Louis. 1945.

for relief of pain in labor, barbiturates and scopolamine being given as first choice. The limitations and disadvantages of the various types of cesarean sections are brought out in the section on obstetric operations. The techniques of extraperitoneal cesarean section are fully illustrated. The author discusses the use of penicillin and the sulfonamides in the various puerperal infections, while the Rh incompatibilities are warned against in the section on transfusion. The volume should provide a quick and practical aid to the solution of obstetric difficulties and emergencies.

PHILIP F. WILLIAMS.

The monograph *The Foetal Circulation and Cardiovascular System, and the Changes They Undergo at Birth* by Alfred E. Barclay, Kenneth J. Franklin, and Marjorie M. L. Prichard³ is outstanding in that it describes the first direct recording of the blood flow in an intact fetus, an experiment which the authors performed in cooperation with Sir Joseph Bancroft and Dr. D. H. Barron.

The authors introduce their subject with a history of the four periods of views concerning the course of the fetal blood flow, including William Harvey's contribution. In the second part of the book they describe the actual course of the blood flow in the mature fetal lamb, as determined by means of cineradiography, a technique which they have perfected. In this section they describe the technique of the necessary operative procedure on the ewe. The method used is contrast media and a radiographic technique. The latter is a refinement and an advancement of the studies made in recent years of the peripheral cardiovascular system.

The third part of the monograph deals with the cardiovascular system and circulation in the mature fetal lamb. Here one finds a glossary of new names which they have substituted in this study for certain parts of the fetal cardiovascular system. The physiologic changes occurring at birth of the lamb are fully discussed. This excellent description of the subject as it relates to the sheep is succeeded by comparative studies in other animals.

The fifth and final part of the book describes the subject as it is applied to the human fetus from our present knowledge of its physiology before birth and the anatomic changes which occur at birth or shortly thereafter. The authors list some of the factors which would complicate a human study of a similar nature. The principal stumbling block to the use in the human of such techniques would undoubtedly be the need for the parents' consent. They suggest, however, that in some such situation as the discovery beforehand that the fetus was abnormal, as an anencephalic monster being diagnosed by roentgen ray, a favorable instance of such a study would be occasioned. There are also discussions in a closing chapter of the various factors concerned with the closure of certain fetal channels. The monograph is a detailed and well-documented study of an important anatomic-physiologic problem.

PHILIP F. WILLIAMS.

In *The Physiology of the Newborn Infant* Dr. Smith⁴ discusses the profound changes and rapid adaptations of the bodily systems at the time of birth. The importance of these adjustments and alterations has been recognized, and here one finds a thorough description of the nature of the changes. In discussing the various systems, the fetal aspect of function is given first to contrast with the neonatal physiology. Of special interest are the chapters on fetal and neonatal respiration. There is an excellent presentation of fetal and neonatal nutrition which describes the assimilation and metabolism of specific food substances, which is followed by an equally important description regarding minerals and vitamins. One is intrigued that the endocrinology of the immediate newborn period has progressed to the high

³The *Foetal Circulation and Cardiovascular System, and the Changes That They Undergo at Birth*. By Alfred E. Barclay, O.B.E., F.R.C.P., F.F.R., F.A.C.R., Kenneth J. Franklin, and Marjorie M. L. Prichard, M.A., of the Nuffield Institute for Medical Research, Oxford Blackwell Scientific Publications, Ltd., Oxford. 1944.

⁴The *Physiology of the Newborn Infant*. By Clement A. Smith, M.D., Professor of Pediatrics, Wayne University College of Medicine; Medical Director, The Children's Hospital of Michigan. First edition. 294 pages. Charles C. Thomas, Springfield, Illinois. 1945.

plane of scientific investigation noted. An important maternal-fetal relationship, in connection with the Rh factor is discussed at some length in the chapter on neonatal immunology.

A helpful feature of the book is a concise and quite practical résumé following each chapter, as a clinical summary. Obstetricians and Pediatricians will find in this volume an excellent discussion of the physiology of the natal period which should be helpful in understanding the problems of the immediate newborn child.

PHILIP F. WILLIAMS.

After seventeen years of publication in three editions Dr. Stone's *The New-Born Infant*,⁵ a manual of obstetric pediatrics, bids fair to becoming an obstetric classic. The aims of this book are to present the pertinent data from the literature, and to emphasize the obstetrician's viewpoint and responsibility for the newborn infant. The present edition is a fine working manual of neonatal physiology and pathology, which expresses concisely the rational principles of care, feeding methods, early diagnosis, and modern treatment. Prenatal influences and birth trauma are the province of the obstetrician; for his benefit the diseases of the neonatal period are thoroughly discussed. The present status of penicillin is mentioned, Rh factor is considered at length, and then there is a review of the hemorrhagic diseases. The care of the premature is detailed. One might wish for more frequent personal opinions by the author. The introduction is an interesting summary of preventive work in obstetrics and pediatrics in recent years. The book should be particularly valuable to the obstetrician who has no pediatrician for his newborn nursery.

PHILIP F. WILLIAMS.

This short monograph⁶ is a doctoral thesis which deals with the ophthalmoscopic and capillaroscopic findings in pregnancy toxemia. These positive findings are supposed to be of great diagnostic help. The thesis is based on nine cases. There are a number of colored charts showing the eye grounds and skin capillary changes.

R. T. FRANK.

Recent Advances in Obstetrics and Gynaecology by Bourne and Williams⁷ is the sixth edition, appearing in three years after the fifth one. Like its predecessors, this is a sterling, well-planned book. Much has been rewritten. Many chapters have been added. Among the new chapters are Nutrition in Pregnancy, Vitamin K, Stillbirth, Neonatal Death, and Erythroblastosis; a chapter on X-ray therapy in gynecology by Levitt, which is now separated from the chapter on Radiological Diagnosis. The chapter on Ovarian Tumors is by Wilfred Shaw, the Radiological Investigation and Diagnosis in Gynecology, by Rohan Williams.

These English books show more coherence and continuity than our American yearbooks. They do this at the expense of not including the more recent literature.

R. T. FRANK.

Perez and Blanchard present a faultlessly gotten up monograph on Vaginal Trichomoniasis⁸ which represents eight years of study. Every aspect of the subject is taken up in detail, with a very thorough presentation of the world literature. Both colored and black and white

⁵*The New-Born Infant. A Manual of obstetric pediatrics.* By Emerson L. Stone, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University; Attending Obstetrician and Gynecologist to the New Haven Hospital. Third Edition. 297 pages. Lea and Febiger, Philadelphia. 1945.

⁶*Patología Vascular de las Toxemias Gravidicas.* Examen oftalmoscópico, capilaroscópico y microscópico postmortem, de los vasos finos de las mujeres con intoxicaciones del embarazo. Por Angel Martínez de La Riva Labarta. 80 pages. Imprenta Moret. La Coruña.

⁷*Recent Advances in Obstetrics and Gynaecology.* By Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. Sixth edition. 77 illustrations. 357 pages. The Blackiston Co., Philadelphia. 1945.

⁸*Tricomoniasis Vaginal.* By Manuel Luis Perez and Oscar Blanchard. 173 pages. "El Ateneo," Buenos Aires. 1944.

illustrations are especially good and instructive. The innumerable methods of treatment which have been published are described, the authors not expressing any very definite personal views as to what they favor. For those who read Spanish, this will prove to be a most instructive monograph.

R. T. FRANK.

Endocrinology

This is an important monograph written by Mme. Moricard,⁹ who, for years before her marriage, had worked with her husband in both the laboratory and clinic. The material is based on six hundred cases studied at the gynecologic clinic of the Hospital Broca. This monograph gives one a summary of the best in French sex endocrinology that has appeared in years. Moricard is known to many of us because he spent some time in traveling throughout the United States and Canada in 1936. His main interest experimentally has been the study of the minute cytology of changes induced by the various sex hormones in the ovary and the rest of the genital tract.

This extensive, well-organized, and well-illustrated monograph of three hundred and eighty-two pages, covers the subject in detail. It goes into the quantitative and qualitative assay of the various hormones, the pharmacology, and then takes up the sex steroids individually.

The second portion deals with the artificial development of the genital tract of the woman, which is based on the careful studies of R. Moricard. The subject of atrophies secondary to hypophysectomy are discussed; then, in detail, the artificial hormonal stimulation of the female genital tract in the human, including artificial menstruation. A good deal of attention is given to disturbances in balance in estrogen and androgen, between estrogen and progesterone, and the symptoms ascribable to these. So-called troubles due to the lack of receptivity, that is, a localized lack of response to hormonal stimuli, is an important and interesting phase of the discussion. Genital dystrophies due to hormonal changes are ascribed to conditions like fibroids, endometriosis, changes in the portio and in the breasts. Particularly attention is paid to contraindications in hormonal therapy.

This is an important monograph, as I have said, which is well worth studying. I naturally find many points of disagreements, but certainly admire the care shown in the detailed studies, the conservative viewpoint, both in making diagnoses and in planning therapy. Anyone interested in sex endocrinology will certainly profit by reading this volume.

R. T. FRANK.

The second edition of Julius Bauer's *Constitution and Disease*¹⁰ has appeared after three years. As the subtitle says, this deals with applied constitutional pathology. Bauer, when professor of medicine at the University of Vienna, attracted a large American post-graduate contingent. His popular appeal continues now that he is professor of clinical medicine in Los Angeles, California. The author states that nothing can "replace the impression gathered from an intelligent observation of the patient himself." Leaving this out of consideration accounts for the fact that frequently patients, who are run through the diagnostic mill in certain clinics, are not benefited by the thorough study because there is a lack of final integration. The object of the book is to stimulate medical thinking, a supplement to the routine medical curriculum. The genetic basis and the tremendous variation in what

⁹*Hormonologie Sexuelle Humaine. Physiologie Pathologie Thérapeutique.* par Mme. F. Moricard. Chargée de la consultation d'endocrinologie de la Clinique gynécologique de Paris. Préface de R. Moricard, Chargé de maîtrise de conférence à la Faculté des Sciences de Caen. Directeur à L'École des Hautes études. 382 pages. Masson et Cie, Paris. 1943.

¹⁰*Constitution and Disease. Applied Constitutional Pathology.* By Julius Bauer, M.D., Professor of Clinical Medicine, College of Medical Evangelists, Los Angeles; Senior Attending Physician, Los Angeles County General Hospital; Consultant in Medicine, Cedars of Lebanon Hospital, Los Angeles; formerly Professor of Medicine, University of Vienna. Second Edition. Revised and enlarged. 247 pages. Grune & Stratton, Inc., New York. 1945.

may be considered normal is emphasized in contradistinction to the similarity noted in uniovular twins in whom even the electric brain waves are either identical or very much alike. Many important subjects are taken up. I instance merely congenital malformations, individual differences in response to the same factors, sex-linked traits. An important chapter deals with constitutional biologic inferiority of the various organs and tissues of the body.

This book is an important and interesting contribution which can be read with great profit by both medical students and practitioners.

R. T. FRANK.

This short monograph¹¹ was accorded the "Madame Durocher Prize" by the National Academy of Medicine, 1944. It is a summary of the quantitative methods of evaluating the gonadotropic and estrogenic hormones. The world literature is given in considerable detail. Concise but understandable directions describing each method are presented. The final chapter includes the method of pregnancy diagnosis.

R. T. FRANK.

Miscellaneous

The March of Medicine¹² is a small brochure which records the ninth year of lectures to the laity. The object of these lectures is to present to the laity through experts and authorities in the field, aspects of medical science which are too often misrepresented in the press, on the radio, and other sources of public information.

Among the subjects dealt with are Morale and Propaganda by Strecker; Food and Civilization by Charles Glen King; a very illuminating talk on the Past, Present, and Future of Chemotherapy by MacLeod; a Survey of Medicine and the Changing World by Fitz; a semi sermon on the Effects of Science upon Human Beings by Sir Gerald Campbell; and a concluding talk on Wars and Epidemics by Lieutenant Colonel Mackie.

These lectures should prove as interesting to the medical profession as to the lay public.

R. T. FRANK.

Stern has written a book on Trauma in Internal Diseases¹³ with consideration of experimental pathology and medicolegal aspects. The author mentions that there are some ten million accidents a year in this country and many of them are allegedly the cause of ensuing internal diseases. War is certainly multiplying the number of such cases. A final responsibility for obtaining fair adjustment of claims, fair to both the injured and to the insurer or taxpayer, is the medical profession. The author hopes that this book will help the practitioner in performing this task.

The entire subject of internal disease is supposed to be covered. This includes not only the infectious diseases but also the diseases of the heart and circulation, of the lungs, in fact, of all the contents of the thoracic cavity. Next are taken up the diseases of the stomach and duodenum, as well as that of the intestine and the appendix; also those of the peritoneum. Subsequently diseases of the liver and the ducts, and diseases of the pancreas and kidney are covered. Malignant neoplasm of the internal organs are dealt with. Then there are diseases of the metabolism, mainly of diabetes, followed by diseases of the endocrine glands. The concluding chapter covers diseases of the blood and lymphatic system.

¹¹Hormônios Gonadotróficos E Estrogênicos. Sua Avaliação Quantitativa. Trabalho lido com o "Prêmio Madame Durocher," pela Academia Nacional de Medicina (1944), by Clarice Do Amaral. 43 pages. Gráfica Sauer, Rio de Janeiro. 1944.

¹²The March of Medicine. The New York Academy of Medicine Lectures to the Laity. 1944. 121 pages. Columbia University Press, New York. 1945.

¹³Trauma in Internal Diseases. With Consideration of Experimental Pathology and Medicolegal Aspects. By Rudolf A. Stern, M.D., Assistant Attending Physician, City Hospital, New York City. Foreword by Francis Carter Wood, M.D., Director of Laboratories and Radiotherapy Department, St. Luke's Hospital, New York. 575 pages. Grune & Stratton, Inc., New York. 1945.

The book is well planned, contains innumerable illustrative cases and case histories, emphasizes the exact pathology, and in some cases quotes court decisions. The material dealt with is extremely large, and is documented by an extended bibliography. From the point of view of our readers, it is noticeable that neither the male nor the female sex organs are considered, although these not infrequently fall into the category of claims following injury. If these omissions were not present, I would consider the book extremely satisfactory.

R. T. FRANK.

The second volume of Dr. Helene Deutsch's *Psychology of Women*¹⁴ on Motherhood is an extremely interesting book. In this thorough psychoanalytic interpretation of womanhood Dr. Deutsch has studied the reproductive process from an entirely new angle. She explains here the emotional factors and conflict situations which come into relation with pregnancy as a whole, and with the organic manifestations characteristic of pregnancy. While many of the psychic problems of pregnant women are difficult of interpretation, the physician will more thoroughly understand the factors which produce them from a study of this text. The attitude of many women toward delivery, and their extreme interest in obstetric analgesia is well discussed in the chapter on delivery. Dr. Deutsch discusses various methods of amnesia and analgesia in labor from the psychologic viewpoint. The related problems of maternity are well considered in the three chapters on the psychologic attitudes of illegitimacy, adoption, and step-motherhood. The volume could be read with profit by all obstetricians.

PHILIP F. WILLIAMS.

This interesting *History of Surgical Anesthesia* by Thomas E. Keyes¹⁵ is an outgrowth of historical research developed for a chronologic table for a recent text on anesthesia. Dr. Chauncey D. Leake has written a delightful introduction to the book, replete with anecdotes and intimate reminiscences concerned in the discovery of recent anesthetic agents. Mr. Keyes goes back through the ages to start his history of anesthesia, and quotes from prose and poetry to give the earliest references to various methods which were used to promote relief from pain. The trials and tribulations in early attempts at inhalation anesthesia and the battles over priority are fittingly illustrated, with excellent pictures of the men of that time, whose names live on today. Mr. Keyes recounts the historical facts associated with development of the various types of anesthesia as we know them today. It appears that scopolamine-morphine was first used in obstetric practice in 1902, and mention is made of other anesthetic methods in obstetrics, including the presently popular caudal block.

The history of anesthetic apparatus is also recorded in the volume. There is an extensive bibliography, and a look into the future by Noel A. Gillespie, which suggests the intellectual opportunities of this still young specialty. The volume should be of interest to all those in the surgical field.

PHILIP F. WILLIAMS.

In this fourth edition of his *Synopsis of Genitourinary Diseases* Dr. Dodson¹⁶ presents essential facts of urology in a concisely styled text for the medical student, and as a handy reference for the physician in practice. The first four of the fourteen chapters in which the text is divided discuss diagnosis, minor procedures, anatomy, and the anomalies. The remainder of the book deals with the various disease of the urological tract. Among the evident revisions to which the previous text has been subjected are the discussions of the sulfonamides in the therapy of urological infection, and the present knowledge of penicillin in

¹⁴*The Psychology of Women. A Psychoanalytic Interpretation* by Helene Deutsch, M.D., Associate Psychiatrist, Massachusetts General Hospital Lecturer, Boston Psychoanalytic Institute. Volume Two, Motherhood. Grune & Stratton, Inc., New York. 1945.

¹⁵*The History of Surgical Anesthesia.* By Thomas E. Keyes. Schuman's, New York. 1945.

¹⁶*Synopsis of Genitourinary Diseases.* By Austin I. Dodson, M.D., F.A.C.S., Professor of Genitourinary Surgery Medical College of Virginia. Fourth Edition. 296 pages. The C. V. Mosby Company, St. Louis. 1945.

similar conditions. The author is quite moderate concerning the use of stilbestrol and castration in the treatment of carcinoma of the prostate. General principles enunciated regarding many topics in this volume should be of value to the obstetrician and gynecologist.

PHILIP F. WILLIAMS.

Dr. Walter L. Bierring has edited the fifth edition of Rypins' Medical Licensure Examinations.¹⁷ The original plan of separate summaries of each subject and actual questions based on the essential facts has been maintained. A new section of Pharmacology has been added. In a foreword Dr. Bierring discusses the philosophy of examinations, which is of interest considering the multitudes of examining boards for both ordinary practices and specialization in this country. Each of the sections into which the text is divided has been reviewed by an outstanding authority on the subject; Dr. Eastman of Johns Hopkins has reviewed the section on Obstetrics and Gynecology. This book is highly recommended for the recent graduate taking State Board Examinations, but it would be of much less assistance to the candidate for a Specialty Board.

PHILIP F. WILLIAMS.

Ribeiro has written a monograph on Lithiasis of the Appendix Vermiformis¹⁸ covering the world's literature, diagnosis, surgical importance, etc. Between 43 and 63 per cent of the cases discovered have been in gangrenous appendices. The author reviewed the Brazilian cases, and adds one case of his own.

R. T. FRANK.

Leon¹⁹ has published a lengthy account of his short incumbency as director general of public health in the province of Buenos Aires. The voluminous and detailed presentation may be of interest to those occupied with public health problems, but has little appeal to the general medical reader.

R. T. FRANK.

¹⁷"Rypins' Medical Licensure Examinations. By Walter L. Bierring, M.D., F.A.C.P., M.R.C.P., Edin. (Hon.). Member, National Board of Medical Examiners; Secretary, Federation of State Medical Boards of the United States; with the collaboration of a Review Panel. Fifth Edition. 530 pages. J. B. Lippincott Company, Philadelphia. 1945.

¹⁸"Lithase do Apêndice. By Eurico Branco Ribeiro, Director do Sanatório São Lucas. 87 pages. Sociedade Editora Médica Limitada. São Paulo, Brasil. 1943.

¹⁹"La Dirección General de Higiene de la Provincia de Buenos Aires. Algo de la labor desarrollada especialmente en el terreno de la Protección Maternal e Infantil. By Dr. Juan Leon. Ex-Director General de Higiene de la Provincia de Buenos Aires. 203 pages. "El Ateneo," Buenos Aires. 1944.

Selected Abstracts

Malignancies

Bromberg, Y. M., and Brzezinski, A.: Primary Melanosarcoma of the Vagina, *J. Obst. & Gynaec. Brit. Emp.* 51: 147, 1944.

The authors report this case of rare tumor of the vagina in a woman 68 years old. The patient was treated with x-ray and radium with improvement for the first six months. The patient developed another tumor on the posterior wall of the vagina. There were no other signs of metastasis in the body. One year after her initial treatment she developed pulmonary metastasis and one month later she developed osseous metastasis and died shortly thereafter.

WILLIAM BERMAN.

Peralta Ramos, Alberto, Albertelli, Jorge F., and Colombo, Emilio: Value of Quantitative Determinations of Gonadotrophin in the Diagnosis of Chorionepithelioma, *Bol. Soc. Chilena de obst. y ginec.* 8: 49, 1943.

The authors state that after eliminating the presence of a pregnancy, the diagnosis of chorionepithelioma may be established without losing time by the search for high values of gonadotrophin: 1,000 rabbit units per liter of serum are enough to indicate hysterectomy, especially if the curve is ascending. Evaluation of the amount of gonadotrophin present after molar pregnancy must be systematic to discover the presence of an active trophoblast capable of degenerating. The evaluation must be made in the serum; adult rabbits must be used for the test, and the unit should be that of Brindeau, Hinglais, and Hinglais.

The authors use the following technique after molar abortion or in cases of suspected malignant degeneration: weekly estimation of gonadotrophin in the serum, searching for 200 rabbit units; if the test is repeatedly negative for two months, the urine is investigated by the concentration method, searching for 50 units which are sufficient to reveal the presence of ovular remnants capable of degenerating. If the result remains negative, the diagnosis of chorionepithelioma is rejected. If in the estimation of the blood the amount of 200 units is found, the tests are repeated weekly to obtain a curve, and if the variation is over 500 units as a minimum, even when the increase in the curve is slow but progressive, the diagnosis of chorionepithelioma is made after elimination of the possibility of a new pregnancy.

J. P. GREENHILL.

Endocrinology

Scheffey, Lewis C., Farrell, David M., and Hahn, George A.: The Role of Injudicious Endocrine Therapy, *J. A. M. A.* 127: 76, 1945.

The authors discuss the use of endoerines in cases of abnormal uterine bleeding without complete physical examination, especially complete pelvic examination. The authors do not wish to discount or disparage the possible benefits of carefully controlled endocrine medication. Its use in the management of functional bleeding of adolescence and in the early reproductive period is permissible providing the patient has been completely and thoroughly examined and no organic reason has been found for the bleeding. When abnormal bleeding is present during the late reproductive, menopausal, or postmenopausal periods, there is much less justification for prolonged and experimental endoerine therapy. Procrastination is inadvisable in these cases. Delayed diagnoses of both benign and malignant conditions of the pelvis are often due to the use of endoerine products without preliminary examination to exclude organic pelvic disease.

WILLIAM BERMAN.

Schaffer, Bernardo: Intravenous Pituitary Extract, *Bol. soc. de obst. y ginec., Chile* 23: 79, 1944.

The experience of the author shows that this procedure is a valuable medication which should only be used on precise indication and in serious cases. Although he does not believe that it jeopardizes the life of the patient, he uses it with caution because he considers it as an active medication which may offer some risks.

It is prudent to replace the intravenous route by injection into the cervix or uterine body when possible. Injection into the cervix is easy; it is sufficient to push the uterine fundus down through the abdominal wall to make the cervix appear at the vulva, especially in multiparas. In any case, it is preferable to use a minor vaginal maneuver to reach the cervix than to inject through the abdominal wall. In cesarean section intramuscular injection is preferred.

If attempts by these routes fail, the intravenous method is indicated to control hemorrhage due to atony which is its principal indication. The method should not be used routinely to separate the placenta because the saving of about fifteen minutes does not compensate for even the remote risk incurred.

J. P. GREENHILL.

Endometriosis

Orfila, J. P.: Diagnosis and Treatment of Endometriosis, Paper presented at the Fifth Argentine Congress of Obstetrics and Gynecology at Buenos Aires, Oct. 3 to 8, 1943.

In this monograph the author takes up all the aspects of endometriosis. He believes that mechanical, irritative, and inflammatory hormonal factors are involved in the etiology. He found endometriosis in approximately 10 per cent of the patients he operated on.

The principal symptoms of endometriosis are pain, which depends on the location of the lesions and includes dysmenorrhea, excessive bleeding at the menses, sterility, and dyspareunia.

Treatment is both prophylactic and curative. Among the prophylactic measures are proper drainage of the uterus, obtained by overcoming cervical stenosis and correcting uterine retroflexions. Active therapy consists of surgical removal of the involved tissue and radiation therapy. The age is an important consideration as to which treatment is chosen. Occasionally, both surgery and radiation must be employed.

J. P. GREENHILL.

Sammartino, R., and Gori, R. M.: Tubal Pregnancy and Endometriosis, *An. brasil do ginec.* 17: 85, 1944.

The authors report a series of 100 cases of ectopic pregnancy studied by serial sections. In 11 cases they found typical endometriosis in the tubes, and in 5 additional cases there were islands of endometriosis associated with the tubal sac. In 31 cases there was a typical decidual reaction. The authors are of the opinion that the incidence of endometriosis in their 100 cases is 42 per cent because they add the cases of decidual reaction to those showing typical endometriosis.

J. P. GREENHILL.

Miller, James Baglan: Preoperative Use of Testosterone Propionate as an Aid to Surgical Treatment of Endometriosis, *J. A. M. A.* 125: 207, 1944.

The author reports a case of endometrioma of the pelvis which bulged into the rectal wall, which was reduced in size by the preoperative injection of 25 mg. testosterone propionate (24 injections given twice weekly). The mass was removed together with the uterus and a portion of the rectal wall which the tumor had invaded. It had not perforated the lining epithelium. The patient made an uneventful recovery.

WILLIAM BERMAN.

Labor

Peiretti, F. S., and Rabinovich, O.: Labor in Breech Presentation, An. ateneo Inst. mat. y asist. 389-403, 1943.

The authors report that breech presentation occurred in 5 per cent of all labors attended to at the Institute during the decade 1934 to 1943. The presentation was complete in 44.1 per cent and incomplete in 55.9 per cent. In the complete form there were 31.8 per cent young primiparas, 8.2 per cent old primiparas, and 60 per cent multiparas; in the incomplete form there were 36.8 per cent young primiparas, 12.2 per cent old primiparas, and 51 per cent multiparas.

Birth was spontaneous in 88.2 per cent: 90 per cent in the young primiparas, 77.9 per cent in the old primiparas, and 89.1 per cent in the multiparas. Birth was spontaneous in 65 per cent of pelvic deformities with breech presentation.

The fetal mortality rate was 19.1 per cent. Elimination of immature, malformed, and macerated fetuses reduced the rate to 10.5 per cent.

The maternal mortality rate was 0.8 per cent, the corrected rate being 0.08 per cent.

J. P. GREENHILL.

Mackie, Margaret A.: Comparison Between Surgical Induction of Labour by Means of the Rectal Tube and Surgical Induction of Labour by Artificial Rupture of the Membranes, M. J. Australia 2: 428, 1944.

This study covers a period of six years, and in each case pregnancy had advanced to at least the twenty-eighth week. The maternal mortality rate in rectal tubal induction was 2.5 per cent while in artificial rupture of the membranes it was 0.5 per cent. Using the accepted standard of morbidity it was found that the rectal tube method of induction gave a morbidity of 17.2 per cent while in artificial rupture of membranes it was 13.5 per cent. The total fetal mortality for tubal induction was 37.2 per cent, while for artificial rupture of membranes it was 19.2 per cent. From 34 weeks' gestation onward the fetal mortality rate is considerably lower when labor is induced by artificial rupture of the membranes, while under 34 weeks' gestation there is no significant difference between the results of the two methods. The time from induction to delivery after artificial rupture of membranes is lower than that after tubal induction in all groups.

WILLIAM BERMAN.

Menopause

Lane, Frederic E.: Menopausal Therapy in Clinic Practice, West. J. Surg. 52: 313, 1944.

A comparison of the clinical response to estradiol benzoate (parenteral) diethylstilbestrol (oral), and hexestrol-phenobarbital (oral) was made on 358 patients with menopausal symptoms. In evaluating results, conclusions were based entirely on subjective response. The estradiol group showed that 83 per cent improved, the diethylstilbestrol group showed improvement in 49 per cent, and the hexestrol group gave a 67 per cent improvement. Best results were obtained with the estradiol group, but the expense of the material and the inconvenience of the injection method caused the authors to adopt the hexestrol-phenobarbital. Their incidence of nausea was 7 per cent and they attribute this low incidence to the presence of phenobarbital in the mixture. Nausea was definitely higher in the stilbestrol group and results definitely inferior.

WILLIAM BICKERS.

Gynecology

Pommerenke, W. T.: Criteria of Ovulation, West. J. Surg. 52: 416, 1944.

A relatively complete history of the evolution of our knowledge relative to ovulation is presented. Man's kinship with other mammals in relation to physiologic changes incident

to ovulation is discussed. The affinity of all the basic science to physiology is emphasized. The means by which this knowledge can be used for the diagnosis of ovulation in the human being are reviewed.

Examination of the corpus luteum at the time of operation gives information as to the probable age of the corpus luteum, and, therefore, the date of ovulation. The theory that ovulation is accomplished by a change in the electric potential between the abdomen and vagina has been used in an effort to determine ovulation time. Normally, the vagina is negative to the abdominal wall by 10 millivolts, and at time of ovulation the vagina becomes positive by 30 millivolts. Various investigators reported conflicting results, and, therefore, it is probably true that a recording apparatus is not sufficiently sensitive to make this a practical clinical procedure.

The rabbit's uterus is extremely sensitive to Pituitrin before ovulation. Following ovulation, the uterus is refractory to pituitrin. Although this is not true in the human being, the pattern of uterine contractions in the human being during the luteal phase is different from that in the follicular phase.

The secretory changes of the endometrium during the luteal phase of the menstrual cycle is the best clinical indicator that ovulation has occurred. The characteristic endometrial picture of secretory phase consists of dilated and distorted glands, stromal edema, vacuolization of the cells, and secretion of the lumen.

Clear, translucent, cervical mucus appears at the time of ovulation in the human. This mucus has been demonstrated to be more permeable to spermatozoa than cervical mucus at other times of the cycle.

The vaginal smear has been used for the diagnosis of ovulation. A sudden increase in leucocytes and cornified cells, particularly when associated with erythrocytes, is diagnostic. By this means the general time, but not the exact moment, of ovulation can be determined.

Cyclic temperature changes occur during the ovulatory cycle in woman. Basal rectal temperatures during the ovulatory cycle show a biphasic curve. During the first half of the cycle, the temperature is relatively low, rising to a peak at ovulation time, followed by a relatively high level during the luteal phase, and dropping again just before menstruation.

From the evidence at hand it appears that ovulation in women occurs about fourteen days before the next expected menstrual period.

WILLIAM BICKERS.

MacFarlane, Catherine, Sturgis, Margaret C., and Fetterman, Faith S.: The Value of Periodic Pelvic Examination, J. A. M. A. 126: 877, 1944.

The authors undertook to determine the value of periodic pelvic examination in the detection of cancer of the cervix in an early stage and also the detection of inflammatory lesions of the cervix which predispose to cancer. A total of 9,111 pelvic examinations were made over a six-year period. During the last two years of this survey the breasts were also examined. In the course of these examinations 18 cancers of 10 different organs were discovered by or reported to the authors. In 461 of the inflammatory lesions found, treatment seemed necessary and was advised in 295 of them, and treatment was carried out in 200 cases. The authors' preference was for the Sturmdorff trachelectomy. The authors are thoroughly convinced of the value of the above procedure in trying to eradicate malignancy.

WILLIAM BEEBMAN.

Pastorini, R., Rabinovich, O., and Chavanne, F. C.: Transfusion of Preserved Placental Blood in the Treatment of Hemorrhagic Metropathies, An. ateneo. Inst. mat. y asist., 323-329, 1943.

The authors claim priority in the use of this method which has a double therapeutic action: specific to cure the endocrine dysfunction, and substitutive to correct the anemia. They recommend trial of the method in all cases of functional metrorrhagia of the puberal, genital, and premenopausal age, with the certainty that no time will be lost for the patient because, even in the worst cases, she will receive the benefit of substitutive therapy.

They report five cases. Three were juvenile metrorrhagias which were arrested by one 150 c.c. transfusion. In two of them the menstrual cycle was again started in regular form. The fourth was a case of Brenecke-Schroeder disease in a woman, 46, with intense anemia: the hemorrhage, which had lasted twenty-two days, stopped four hours after a 200 c.c. transfusion. The fifth case was that of a woman, 25 years of age, with acute anemia caused by a hemorrhage occurring after an amenorrhea of three months. Histologic study revealed an atrophic uterine mucosa. The hemorrhage, which had lasted several days, decreased markedly after a first transfusion of 320 c.c., and stopped after a second transfusion of 250 c.c. given thirty-six hours after the first.

J. P. GREENHILL.

Menstruation

Soares Baptista, J. A.: Premenstrual Tension, *Rev. de gynec. e d'obst.* 38: 19, 1944.

In five cases, the author used the therapeutic method of Greenhill and Freed who obtained good results by eliminating salt from the diet and giving ammonium chloride, 0.60 Gm. three times a day, during the second part of the menstrual cycle.

In four patients the author obtained disappearance of the syndrome during the period of treatment. But the treatment gave little or sometimes no relief in the remaining patient who had a grave form of tension. Therefore, the advice of Frank was followed and the ovaries were irradiated to obtain temporary castration; this made all symptoms of tension disappear as long as the action of the rays lasted.

Bromides were administered as adjuvants during the worst days of tension.

J. P. GREENHILL.

Item

American Board of Obstetrics and Gynecology, Inc.

The following diplomate has been certified and is added to the previously published list: Dr. Max L. Berlowe, 315 Whitney Avenue, New Haven, Connecticut; born 1907; received M.D. from Long Island College of Medicine in 1934.

Paper in This Issue

Due to conditions beyond the control of the editors and publishers, this issue of the JOURNAL is printed on uncoated paper.

Correspondence

The Extraperitoneal Cesarean Section

To the Editor:

In his article (AM. J. OBST. AND GYN. 50: 191, 1945) Bourgeois states: "Extraperitoneal cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor." Few will find such a statement objectionable. Probably, few will consider Bourgeois' technique as "extraperitoneal." Few, very few, obstetricians will read the details of his case reports without being somewhat astounded. Some will wonder whether the description of a technique and the invention of a word to describe it will ever adequately replace sound obstetric judgment and reasonable obstetric courage.

Bourgeois presents ten brief descriptions of cases in which his technique was employed. In eight of these, from data presented by the author, reasonable indication for *elective* section was manifest at the time the cases were admitted to the hospital. In the other two cases certain facts are not presented and it is entirely possible that if they were included in the paper those cases too might have presented indications for elective section.

We have listed Bourgeois' cases, with his data, following each with a brief comment.

CASE 1.—"26-year-old primigravida . . . entered the hospital in early labor, roentgenologic examination disclosed a small gynecoid pelvis with evidence of cephalopelvic disproportion." The alternative to elective section in the presence of a small gynecoid pelvis is test or trial of labor. This patient was allowed 19 hours of "strong labor" twelve of them with the membranes ruptured. Why? Was it a trial of labor or endurance?

CASE 2.—". . . a small gynecoid-android pelvis with much molding of the unengaged head." In place of elective section this patient labored for 27 hours before section was performed. Why?

CASE 3.—". . . diagonal conjugate had measured 9.5 cm., and x-ray had disclosed a platypelloid pelvis." (This patient had previously delivered a baby spontaneously. The baby died in the neonatal period.) "After 10 hours of moderate labor without promise of engagement of the overriding head, pregnancy was terminated . . . by cesarean section, by election of the extraperitoneal type."

This patient, having had one baby die, presented a bad pelvis and an unengaged vertex. In place of prompt section, the baby was risked through 10 hours of labor. The condition of the membranes is not stated, but it is obvious enough that this patient did not require extraperitoneal section.

CASE 4.—"A 35-year-old primigravida . . . small gynecoid pelvis. Going into labor at thirty-nine weeks' gestation with a frank breech." This is sufficient indication for elective section for most obstetricians. The indication was not noted. Instead: "she made satisfactory progress until the cervix was completely dilated, after which the breech failed to advance during a nine-hour period." Is this to be believed? In 1945? Nine hours of the second stage of labor before intervention?

CASE 5.—"A 25-year-old primigravida . . . with a small gynecoid pelvis by both clinical and x-ray examination." This patient presented an unengaged vertex. Again reasonable indication for elective section or humane trial or test of labor. The author noted, "failed to engage the head after 27 hours of labor and eight hours of membrane rupture." He then delivered by extraperitoneal section (his technique) an 8-pound 12-ounce baby. A large baby and a small gynecoid pelvis call for elective section, not 27 hours of aseptic torture.

CASE 7.—“A 26-year-old primigravida . . . presented a small platypelloid pelvis with diagonal conjugate of 9 cm. . . the head persistently overrode the symphysis.” Cesarean section on admission to a hospital in such a case would evoke no criticism. The author did not determine in a matter of seconds by such a procedure as the “Hillis Impression” that the “head persistently overrode the symphysis.” His patient was in labor for 17 hours before he decided upon section.

CASE 9.—“A 23-year-old primigravida at term presented an unengaged head after 38 hours of labor and an equal duration of membrane rupture.” If this patient was admitted to the hospital in the first hours of labor, section should have been performed at the end of 4 to 6 hours, at the very latest.

CASE 10.—“A 28-year-old primigravida at thirty-nine weeks' gestation entered the hospital in early labor with a frank breech presentation. The membranes had ruptured 2 hours after the onset of labor. The cervix was completely dilated and the breech in midpelvis after 9 hours of labor . . . *no further descent of the breech occurred during the next five hours,** sterile vaginal examination was performed. It revealed firm soft tissues and a gynecoid pelvis which seemed adequate except for a contracted outlet.”

Fourteen hours after the onset of labor the status of the pelvis is first discovered. The second stage of labor is permitted to continue for what must be a world's record of 13 hours. Only then, after 13 hours of the second stage is intervention considered. This is a little too much to expect even from the wives of soldiers, or possibly the Army puts the wives through some sort of training to prepare them for such a monstrous ordeal.

Cases 6 and 8 were in labor 46 and 80 hours, respectively, before decision to operate was arrived at.

It is difficult to classify in obstetric terms or practice, the conduct of the reported labors. Radical obstetricians would have proceeded to elective section almost immediately after encountering such cases. Certainly that is the method we would have chosen. More conservative obstetricians would have allowed a 12- or 14-hour test or trial of labor only if the membranes were intact, and in the face of a ruptured sac such workers would limit their tests or trials to four to six hours.

Bourgeois' management is on no happy middle ground. It most resembles a studied neglect, a conduct of labor creating a situation in which the only choice permitted to remain possible was no choice at all; the only thing left to do was extraperitoneal section. Such management is not unheard of. We have had residents who employed similar schemes when they were trying to acquire operative experience but they limited themselves to less explosive situations. If the described conduct of labor was not aimed toward obtaining material for extraperitoneal section, how can trial or tests of labor of 19, 27, 10, 27, 17, and 38 hours be explained? How can two second stages of 13 and 9 hours be explained?

“Extraperitoneal cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor.” No truer than this: that it is better to prevent potential or actual infection; that that it is better to recognize obstructed labor early; that it is better to come to a decision within reasonable and humane time limits; that in the course of practice, unfortunately, there will occur the infected cases with obstructed labor to which the extraperitoneal technique will be genuinely applicable. Unfortunately, there will be no need to create material for its application.

(Signed)

FRED. A. KASSEBOHM, M.D., F.A.C.S.
MILTON J. SCHREIBER, M.D., F.A.C.S.

272 WEST 90 STREET
320 CENTRAL PARK WEST

*Italics mine.

Reply by Major Bourgeois

To the Editor:

I have reviewed the communication of Drs. Kassebohm and Schreiber concerning the article, "A Peritoneal Staining Technique for Extraperitoneal Cesarean Section," which appeared in the August issue of the JOURNAL. They admit that they have no quarrel with extraperitoneal cesarean section per se, and they offer no direct criticism of the peritoneal staining technique.

The essence of their criticism is (1) that I have allowed parturients presenting a reasonable doubt as to the ultimate necessity for cesarean section to demonstrate their potentialities by a so-called test of labor, and (2) that I have electively exhibited the extraperitoneal operation.

Regarding the first point, it is germane to state that two divergent schools of thought concerning cesarean section exist. One believes that the need for section can be prophesied with certainty prior to the onset of labor. The other believes that because unpredictable factors such as distensibility of the maternal pelvic joints, molding of the fetal head, and the character of labor enter the picture, any patient presenting questionable or relative but uncomplicated disproportion deserves an opportunity to demonstrate her ability in actual labor. It has been my experience to see many such patients deliver uneventfully from below. My critics make it clear that they belong to the first school of thought; I belong to the second.

Still regarding the first point, it is generally accepted at the present time that maternal mortality following cesarean section is from five to ten times greater than maternal mortality following vaginal delivery. The incidence of maternal morbidity following section is probably greater in at least the same degree. Furthermore, effacement of the cervix and the taking up of the lower uterine segment consequent to a few hours of labor favors technical ease, and, what is even more important, the conservation of blood in any lower segment operation; these factors serve to make cesarean section safer.

Regarding the second point, I stated in the original article that two extraperitoneal cesareans had been performed electively to augment experience with the peritoneal staining technique. It was also clearly stated that the indications set forth by Drs. S. A. Cosgrove and J. F. Norton of the Margaret Hague Maternity Hospital had been followed in the other eight cases presented. Dr. E. G. Waters of the same clinic informs me (personal communication) that in approximately 300 extraperitoneal cesarean sections of his type performed by 28 operators there occurred 2 deaths. This cesarean mortality is lower than that reported for almost all comparable series of elective transperitoneal operations. Following the tenets of the three above-mentioned obstetricians I have performed cesarean section of all types 27 times in a total of 1,125 consecutive deliveries during the past thirty-one months at the AAF Regional Station Hospital, Mitchel Field, New York, a cesarean incidence of 2.4 per cent. There have been no cesarean deaths.

I leave it to the readers of this JOURNAL whether I am humane in allowing patients with relative fetopelvic disproportion a test of labor with appropriate sedation, and with the result that many doubtful cases deliver by vagina spontaneously or with the aid of simple forceps maneuver; or whether my critics, who manifestly foresee the outcome of such cases prior to labor and subject their patients to what must be a much higher cesarean incidence with its concomitant increased incidence of maternal mortality and morbidity, are more humane. The late Dr. DeLee often inquired, in effect: "How much pain is worth the life of one mother or one baby?"

The foregoing statements are my answer to Drs. Kassebohm and Schreiber from the professional point of view. Their precipitate and unfounded implications concerning Army obstetrics in general, and concerning me in particular, do not merit the dignity of a reply.

(Signed) GEORGE A. BOURGEOIS, MAJOR, M.C.

Chief of Section of Obstetrics and Gynecology

AAF REGIONAL STATION HOSPITAL
MITCHEL FIELD, NEW YORK

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Edward A. Schumann, Philadelphia, Pa. *Secretary*, Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting to be announced later.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888). *President*, Lewis F. Smead, Toledo, Ohio. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1946.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting Chicago, Ill., October, 1946.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting to be announced later.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Philip F. Williams, Philadelphia, Pa. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas Tex. Annual meeting San Francisco, July 1-7, 1946.
- New York Obstetrical Society.** (1863) *President*, R. A. Hurd. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Bernard Mann. *Secretary*, John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, James E. Fitzgerald. *Secretary*, Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, John J. Madden. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fair, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Charles Hunt. *Secretary-Treasurer*, Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James S. Taylor. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, George Van S. Smith. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Roy J. Heffernan, Brookline, Mass. *Secretary*, Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Goodrich C. Schaffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

- New Orleans Obstetrical and Gynecological Society. (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society. (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society. (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists. (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Robert B. Kennedy. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals. (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists. *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society. *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society. (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society. (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology. (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society. (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology. (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society. (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Schamberger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society. (1944) *President*, Sylvester Goodman. *Secretary*, Zeph J. B. Hollenbeck, 9 Buttrick Ave., Columbus, Ohio. Meetings held last Wednesday of each month.
- Nassau Obstetrical Society. (1944) *President*, Arthur C. Martin. *Secretary*, William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bi-monthly from October to May.
- Bronx Gynecological and Obstetrical Society. (1924) *President*, Jacob Clahr. *Secretary-Treasurer*, J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society. (1936) *President*, John H. Fiorino. *Everett*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society. (1922) *President*, J. Milton Singleton. *Secretary*, Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.
- Los Angeles Obstetrical and Gynecological Society. (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society. (1932) *President*, Frank Locke, Winston-Salem. *Secretary*, Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.

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DERMOID CYSTS OF THE OVARY: THEIR CLINICAL AND PATHOLOGIC SIGNIFICANCE*

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TO MANY the term "ovarian dermoid" cyst denotes merely a ball of hair invested by a mantle of ectodermal tissue occasionally supporting one or more teeth. Careful examination, however, frequently reveals a variety of tissues including bone, cartilage, smooth muscle, fat, and so forth, all of which make rather indefinite the dividing line between this type of tumor and members of the more complex teratoma group. Although many papers have been published on ovarian dermoids, these contributions to the medical literature have, for the most part, been based on a study of a single case or a small series of cases.^{4, 18, 21, 25} With the feeling that a review of a large group of these tumors might produce some valuable information, the present study was undertaken with the following questions in mind: namely, what are the usual histologic components of the tumors and how many tumors are truly monodermal? Are the symptoms and signs produced diagnostic of the tumor type? What is the incidence and what are the types of malignant transformation seen in ovarian dermoids?

Historical Data

Except for one outstanding article by Pauly²² in 1875, a review of the literature reveals a surprising lack of historical material on such an important

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subject as dermoid cysts of the ovary. The following depicts in more or less chronologic order the data obtained from an extensive review of the writings on this subject.

One of the earliest medical records of a dermoid cyst of the ovary was made by Johannes Scultetus²⁷ in 1659. His notes and illustrations of a necropsy are said to be convincing evidence that he was describing such a tumor. Lebert¹⁶ is credited with first applying the term "dermoid cyst" to all cysts lined by a structure resembling skin, but in 1831 Leblanc¹⁷ had described what he called a "kyste dermoid" at the base of the skull of a horse. Kohlrausch,¹⁴ in 1843, had described the microscopic appearance of a "kyste dermoid," drawing attention to the analogy of its structure to that of the skin, so that when Lebert published his work in 1853, he had but one step to take to apply the term "dermoid cyst" to this entire group of neoplasms.

From gross examination, it was long evident that these cysts usually contain hair and frequently teeth and bone, but sudoriferous glands were not described until 1843 by Kohlrausch. Ten years later, Gray¹⁰ noted nerve fibers and ganglion cells, unaware that Steinlin²⁸ had discovered nerve tissue in a dermoid cyst three years previously. In 1859, Virchow²⁹ found a cerebellum-like structure. He is also credited with discovering smooth muscle fibers which he considered as "arrectores pilorum." Virchow has been quoted as having found striated muscular fibers in dermoid cysts of the ovary, but Pauly read the original articles of Virchow to find that, although striated muscle was described, the cysts were not dermoid in character.

In 1860, Salter²⁵ found nerve in the pulp of the teeth in these tumors. In the same year Heschl¹² reported several pieces of bone connected by a false joint lined by periosteum. In 1888, Bland Sutton⁴ found well-developed mammary glands, and in 1890, Pommer²³ described tissues resembling cecum and appendix. By 1895, Wilms³⁰ had written of thyroid tissue in a dermoid cyst. In 1906, Schottlaender²⁶ called attention to the frequent association of corpus luteum cysts in the walls of dermoids and stated that these were frequently overlooked. Boyd⁶ has found a well-developed adrenal in one of these neoplasms. Kordi¹⁵ recognized a lens and eyelid. Key¹³ found salivary glands near the maxillary bone which occurred in a dermoid, and Wilms³¹ described a rudiment of lung.

Etiology

Many hypotheses have been advanced to explain the origin of these tumors, and some of them will be listed: hair eaten by the patient and localized to the ovary; nightmares; witchcraft; a judgment of the Deity on immoral practices; unsatisfied sexual longings; metaplasia of Pflüger's tubules; extrauterine or ovarian pregnancies; inclusion of external integument; Graafian follicles; degeneration of a fertilized ovum; imperfect or diseased tubes incapable of receiving an ovum; cell rests; production of secondary embryonic site in the primitive streak; fertilization of primordial ovum in a growing embryo; misplaced blastomere; parthenogenetic development of ovum.

Many of these explanations appear to be ridiculous and others may or may not be correct. It was formerly held that these cysts resulted from a fertilized ovum and many young girls were falsely charged with social transgressions until Baillie² published his belief that there need be no previous connection with a male and that these tumors "arise from some action within the ovarium itself which is imitative of generation." Cohnheim⁷ expressed the belief that there are numerous embryonal tissues not utilized during development and these may give rise to all types of neoplastic formations. The teratoma is one of the strongest arguments in support of this hypothesis.

Most of the discussion today centers around the last two listed hypotheses. Bonnet⁵ has shown that, if an ovum is agitated, a blastomere can become dislodged and result in the formation of a potential second individual. Also in the process of segmentation, cell elements may wander or become displaced to develop later after a period of quiescence. Murray²⁰ transplanted the blastoderm of the chick. He found that when the entire blastoderm was grafted, the degree of histologic differentiation was comparable to that found in normal chicks of an equivalent age, but when partial grafts were used, the degree of differentiation fell short of this and appeared similar to that of teratomas. Holtfreter^{12,a} killed all the cells of a morula of Triton except four and kept these alive in modified Ringer's solution. In nine days, the four cells had produced an irregular elongated body not unlike a teratoma. The following tissues were present: epidermis, nervous tissues, skeletal muscle, a piece of notochord, and an otic vesicle. This evidence firmly supports the blastomere hypothesis but should there be such a predilection for these to be present in the ovary? One would expect to find the cystic teratomas indiscriminately throughout the entire body.

Parthenogenesis or asexual reproduction has been observed in lower animals. Piercing the ovaries of a frog with a needle sometimes results in the development of complicated teratomas. It is recognized that these tumors occur during the period of functional activity of the ovaries. If, however, it was possible for a teratoma to spring from an unimpregnated egg, one would expect a much greater frequency of these tumors, especially in the tube, than has been observed. Less than twelve have been reported. This would account for the great preponderance of these tumors in the ovary.

The experimental production of ovarian dermoids has not been accomplished in warm-blooded animals. However, Michalowsky,¹⁹ Bagg,² Falin,⁸ and Falin and Gromzowa⁹ have produced neoplasms of comparable structure in the testes of the adult rooster using zinc chloride and zinc sulfate as the initiating agents. Age and seasonal variations in sexual activity appeared to act as modifying influences in the success of their experiments, the interpretation of which, as related to the origin of ovarian dermoids, is at present obscure.

The number of hypotheses advanced to explain the origin of these neoplasms merely confirms the fact that knowledge concerning their cause is still conjectural.

Material and Methods

For the purpose of this study, the records in 225 consecutive cases of dermoid cysts of the ovary removed at operation in the Mayo Clinic were reviewed. One hundred consecutive tumors of this group were examined macroscopically, and from ten to fifteen sections were removed from the cyst wall for microscopic study. In a few instances, the size of the tumor permitted the selection of only two to five sections, but in every cyst, these sections were taken at scattered areas in order that the structures of the cyst wall should be well represented. These tissues were routinely stained with hematoxylin and eosin. To

demonstrate mucus, the Galantha mucus stain was used. Many of the sections contained bone or calcium and for these the Galantha method for rapid decalcification was employed. To demonstrate myelin sheaths of nerves, the Bodian stain was chosen.

Results

Incidence.—The incidence of dermoids is usually stated to be about 10 per cent of all ovarian neoplasms, but the incidence in this series was only about 5 per cent. There was no predilection for either ovary. Twelve and four-tenths per cent were bilateral (Table I).

TABLE I. LOCATION OF DERMOID CYSTS

LOCATION	NUMBER	PER CENT
Right ovary	99	44.0
Left ovary	96	42.7
Bilateral	28	12.4
Unrecorded	2	0.9

TABLE II. INCIDENCE AS TO AGE

AGE (YEARS)	TUMORS
6-10	3
11-15	1
16-20	6
21-25	15
26-30	32
31-35	36
36-40	38
41-45	38
46-50	27
51-55	23
56-60	14
61-65	8
66-70	10
71-75	2

These cysts were found in patients of all ages (Table II), but no proof was forthcoming that they arose after the menopause. The consensus is that the tumors discovered late in life arose before cessation of ovarian activity. The youngest patient in this group was 7, and the oldest, 72 years of age. Approximately 85 per cent of these tumors were removed from patients between the ages of 16 and 55 years. The incidence was therefore greatest during the reproductive life of the patient.

There was no apparent relationship between the average size of the cysts and the ages of the patients (Tables III and IV).

Gross Appearance.—On gross inspection these cystic masses were smooth and glistening, but, after removal from the body and exposure to the air, the surfaces became wrinkled, stiff, and dull. The shape usually was globular but sometimes was ovoid. The color was, generally speaking, milky white, although the yellow color of the contents was often noted through the wall. Discoloration by blood pigment was found only after torsion of the pedicle. The tumor was soft and cystic at body temperature unless the wall was calcified or contained bone, ear-

TABLE III. AVERAGE SIZE OF DERMOID CYST AS RELATED TO AGE OF PATIENT

AGE (YEARS)	SIZE (CM.)
6-10	9.0
11-15	6.0
16-20	12.5
21-25	9.6
26-30	7.1
31-35	8.0
36-40	7.8
41-45	7.4
46-50	9.4
51-55	7.6
56-60	8.8
61-65	16.0
66-70	8.0
71-75	4.5

TABLE IV. INCIDENCE AS TO AGE OF PATIENT AND SIZE OF TUMOR

SIZE OF TUMOR (CM.)	AGE OF PATIENT (YEARS)														
	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80
1					1	1	1	2	1					1	
2					1	2		2	3					2	
3			1		3	4	2	3	1	2	1				
4					1	2	3	4	1	4	1				1
5	1			2	4	1	2	5		1	1	1			1
6		1			4	5	5		2	2	1	1		1	
7	1				8	4	4	1	1	3	1			1	
8			2	4	4	2	6	6	3	3	1	1		1	
9				1	3	6	6	4	2	3	4			1	
10				1			4	3	3	4					
11				1		1		2	1		1				
12					1			3	1	4					
13				2	1			1	2	1	1				
14				1						2	1			1	
15	1		1	2		1	2	3				1		1	
16			1	1		1					1			1	
17									1			1			
20						1									
23												1			
24									1						
25			1						1			1			
27						1						1			
30					1										

tilage, or teeth. (Although surmised previously, it was not until 1859 that a necropsy, performed while the body was still warm, proved that the fatty contents of a dermoid cyst existed in fluid state during life.) As the contents cooled to room temperature, they became a doughy, semisolid mass. The oily material was composed of fat, desquamated epithelium, glycerides of fatty acids, cholesterol, and other alcohols, a mixture of materials which becomes liquid at temperatures above 34° C. but solidifies at temperatures below 25° C. In this yellow, oily substance were tangled masses of hair and frequently teeth and bone. From the inner surface of the wall, there usually projected a white, shiny protuberance to which numerous hairs were attached. The remainder of the wall was sometimes smooth as in a simple cyst and sometimes granular as in an old abscess cavity. The cyst was usually unilocular, although 12 per cent of this group were multilocular. Multiple dermoids were not present.

The rounded mass projecting from the wall into the cyst cavity, variously known as the dermoid plug, Rokitansky's protuberance, focus, dermoid process, mamilla, or pseudomamma, was found in variable relation to the pedicle of the dermoid. In some cysts it existed as only a thickened portion of the wall, in others as a prominent protuberance varying in size and irregularity and in several it was present as a bridge across the cyst cavity. Occasionally more than one dermoid process was present and in one of this series, four were noted within one unilocular dermoid cavity.

The protuberance was frequently covered with hair and contained bone, cartilage, and teeth. The hair was not always of the same color as that on the head of the patient. Sometimes it was long and coarse and sometimes short and fine as lanugo. The longest hair in this series was 27 cm. While examining the tumors, hairs would be found which at first appeared to be more than 50 cm., but on careful handling it was found that these were only several shorter hairs matted together by the oily contents of the cyst. Much of the hair was broken, lying free within the cyst. The color was brown, black, blond, gray, red, or snow-white, and it was not uncommon to find more than one color in the same dermoid. In bilateral cysts, the color of the hair was frequently different in the two cysts. The color of the hair bore no relation to the age of the patient. In several of the specimens studied, hair was not evident grossly, but on microscopic examination, all but one demonstrated hair follicles in the cyst wall.

Teeth occurred with a frequency exceeding that which one would expect from reading current reports. In this series, teeth were present in 31 per cent of the cases. In four of these, the teeth were not erupted and were not discovered until the tumor was dissected. They resembled adult incisors or molars, rarely canines, but their development was not related to the age of the patient. The roots were single in all but two and these were bifurcated. The enamel and dentine were distinctly formed. Heschl¹¹ found carious teeth in a necrotic tumor, but no caries was evident in any of the teeth examined in this group. The teeth were usually embedded in the wall or occasionally implanted in a rudimentary maxilla or mandible but in three instances they were found free in the cyst cavity.

Phalanges of a finger, rudimentary parts of both extremities, ribs, sternum, pelvis, and even an incomplete skeleton have been reported, but these were not identified in any of the neoplasms dissected.

Repeated examination of patients, who at first had refused surgical treatment or postponed the operation for months or even as long as eight years, indicated that the tumors were of slow growth. They seldom attained a size greater than 16 cm. (Table V), the largest in this series being 30 cm. and the smallest 8 mm. in diameter. The average size is 8.2 cm.; the bilateral tumors average 7.75 cm. in diameter. There is little difference in size as to location, those arising from the right ovary averaging 8.4 cm., those from the left averaging 8.0 cm. in diameter.

Microscopic Findings.—Microscopic examination showed the structure of the dermoid cyst to be more varied than suggested by the appearance on gross examination (Table VI). The cyst wall was thicker than that of other ovarian

TABLE V. INCIDENCE AS TO SIZE OF TUMOR

SIZE (CM.)	TUMORS
1	7
2	10
3	17
4	17
5	19
6	22
7	24
8	33
9	30
10	15
11	6
12	11
13	9
14	5
15	12
16	5
17	2
20	1
23	1
24	1
25	3
27	2
30	1

TABLE VI. INCIDENCE OF STRUCTURES OBSERVED MICROSCOPICALLY

STRUCTURE	PER CENT
Stratified squamous epithelium	100
Sebaceous glands	97
Hair follicles	99
Apocrine glands	47
Sweat glands	64
Brain	37
Nerve	47
Ganglion cells	19
Ependymal cells	25
Teeth	31
Cartilage	27
Bone	41
Smooth muscle	74
Fat	75
Lymphocytes	51
Foam cells (pseudoxanthoma)	55
Giant cells	61
Thyroid	13
Gastrointestinal tract epithelium	12
Respiratory tract epithelium	53
Salivary glands	16
Ovarian tissue	91
Adult lung	2
Fetal lung	1
Brenner tumor	1
Oligodendroglial tissue	1
Carcinoid	1
Squamous-cell epithelioma, grade 3	2
Nodes of Ranvier	1
Retina	2
Pancreas (?)	1
Prostate	1

cystomas. Derivatives of ectoderm were evident in 100 per cent of the tumors. The interior was lined by stratified squamous epithelium which resembled skin although there was no tendency to the production of a horny layer. Papillae were small and were often absent. No "touch corpuseles" were identified. There was a tendency for the stratified epithelium to become thinner in the portion of the cyst farthest from the dermoid process (Fig. 1, *a*) and in some instances squamous epithelium was lacking in portions of the cyst (Fig. 1, *b*). These denuded areas were composed of granulation tissue with pseudoxanthoma cells and frequently foreign body giant cells. Localized areas of lymphocytic infiltration appeared beneath the stratified epithelium in 46 per cent (Fig. 1; *c*).

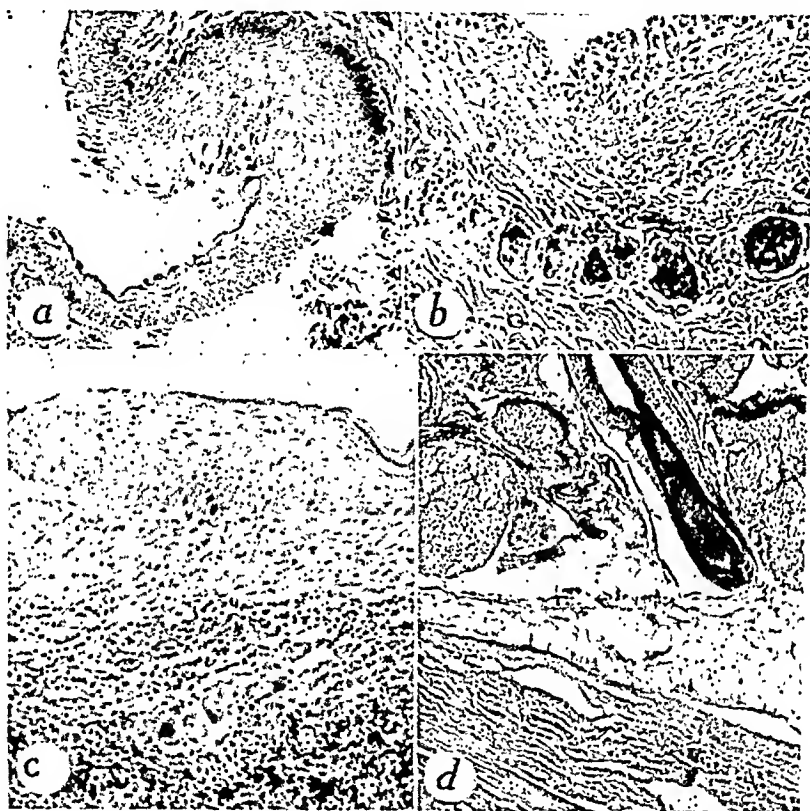


Fig. 1.—Ovarian dermoid cyst showing: *a*, Thinning of stratified squamous epithelium ($\times 100$). *b*, Foreign body type of giant cells. Overlying squamous epithelium has been destroyed. Pseudoxanthoma cells are also seen ($\times 85$). *c*, Localized areas of lymphocytes beneath the lining epithelium ($\times 95$). *d*, Well-developed sebaceous glands and hair follicle ($\times 32$).

Hair follicles were present in 99 per cent (Fig. 1, *d*) and were well formed even in the absence of grossly recognizable hair.

Typical sebaceous glands were found in 97 per cent (Fig. 1, *d*). It was felt that these are chiefly responsible for the presence of the oily, sebaceous contents of the cyst.

Sudoriferous glands were present in 64 per cent of this series (Fig. 2, *a*). Apocrine glands were noted in 47 per cent of the cysts (Fig. 2, *b*). Both types of glands were well formed.

Brain substance was recognized in 37 per cent of the group and constituted one of the most interesting types of tissue in this study. Fig. 2, *c* shows an attempt at convolutions of the cerebellum. Well-developed Purkinje fibers were



Fig. 2.—Ovarian dermoid cyst showing: *a*, Section through coiled sweat glands ($\times 100$). *b*, Apocrine and sweat glands. Sebaceous gland and cross section of hair follicle also illustrated ($\times 95$). *c*, Convolutions of cerebellum. The three strata are distinct ($\times 42$). *d*, Oligodendroglial tissue simulating an oligodendroglioma ($\times 100$).

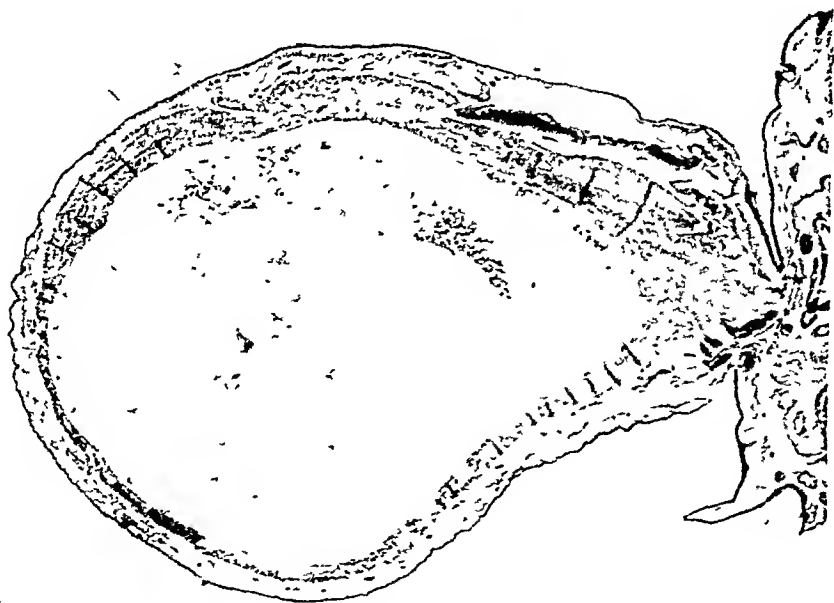


Fig. 3.—Structure simulating the optic vesicle ($\times 9$).

present in two cases. Fig. 2, *d* reveals oligodendroglial cells, which are suggestive of an oligodendroglioma. Calcification of the brain tissue, in the absence of calcium deposits elsewhere in the cyst wall, was present in 7 per cent. Areas resembling retina were found in two cases, one occurring in connection with what apparently was a rudimentary optic vesicle (Fig. 3). Ependymal cells were identified in 25 per cent of the tumors and in two instances areas typical of choroid plexus were seen (Fig. 4, *a*).



Fig. 4.—Ovarian dermoid cyst illustrating: *a*, An area typical of the choroid plexus ($\times 100$). *b*, Ganglion cells and nerve fibrils ($\times 65$). *c*, Sheets of smooth muscle fibers ($\times 80$). *d*, Marrow-containing bone ($\times 13$).

In forty-seven of these tumors, nerve fibers were identified and these were of the nonmedullated type with but one exception, which clearly exhibited the myelin sheath and nodes of Ranvier. Ganglion cells were present in nineteen of the cyst walls (Fig. 4, *b*).

Mesodermal elements were common, occurring in 93 per cent of this group. Smooth muscle was present in 74 per cent, usually as localized bundles, although sheets of muscle tissue were frequently encountered (Fig. 4, *c*). Striated muscle fibers have been reported but never confirmed. None were identified in our material.

Bone was represented in 41 per cent, and half of these exhibited marrow (Fig. 4, *d*). In three cases the bony structure supported teeth and resembled

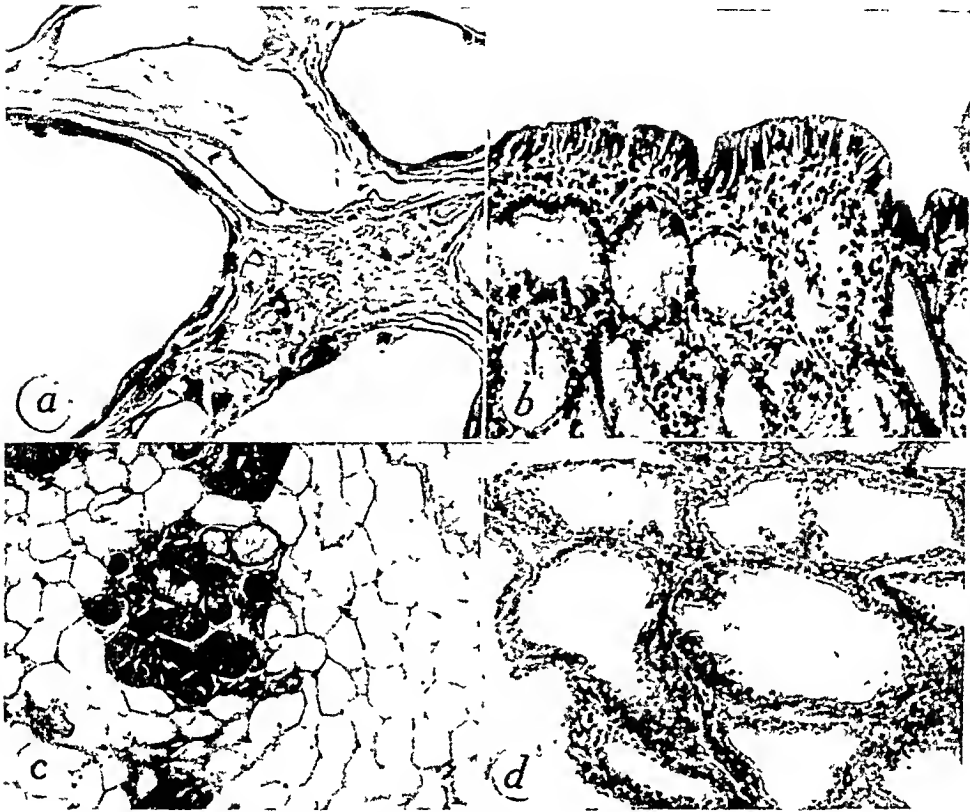


Fig. 5.—Ovarian dermoid cyst illustrating: *a*, Cystlike spaces lined by giant cells ($\times 100$). *b*, Epithelium resembling the gastric mucosa ($\times 120$). *c*, Salivary gland of mixed mucous and serous type ($\times 60$). *d*, Tissue resembling fetal lung ($\times 100$).

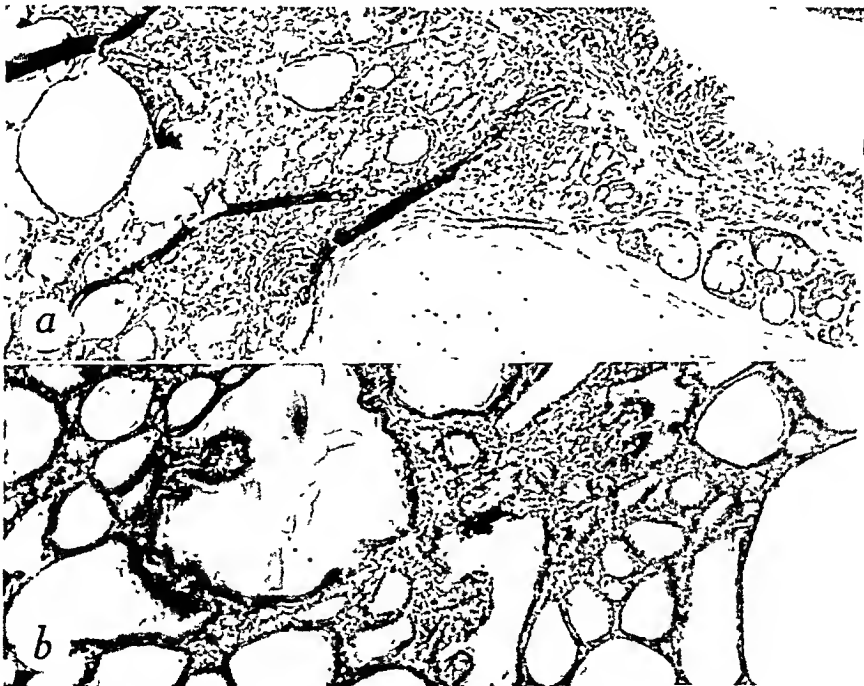


Fig. 6.—Ovarian dermoid cyst illustrating: *a*, Respiratory tract type of epithelium tracheal glands, cartilage, and thyroid ($\times 55$). *b*, Thyroid tissue with parenchymatous hypertrophy ($\times 60$).

that of the maxilla; in one there was a likeness to the mandible. Thin plates of bone, as found in the skull, were present occasionally but one could not say that any of these formations were definitely like that of the adult skeleton.

Frequently, sievelike areas separated by thin partitions of fibrous tissue were found. These cystlike spaces were lined by giant cells (Fig. 5, *a*). This condition has been thought to represent an undifferentiated epithelial tissue or foreign body giant cells, but in any event it seems to be pathognomonic of dermoid cyst of the ovary.

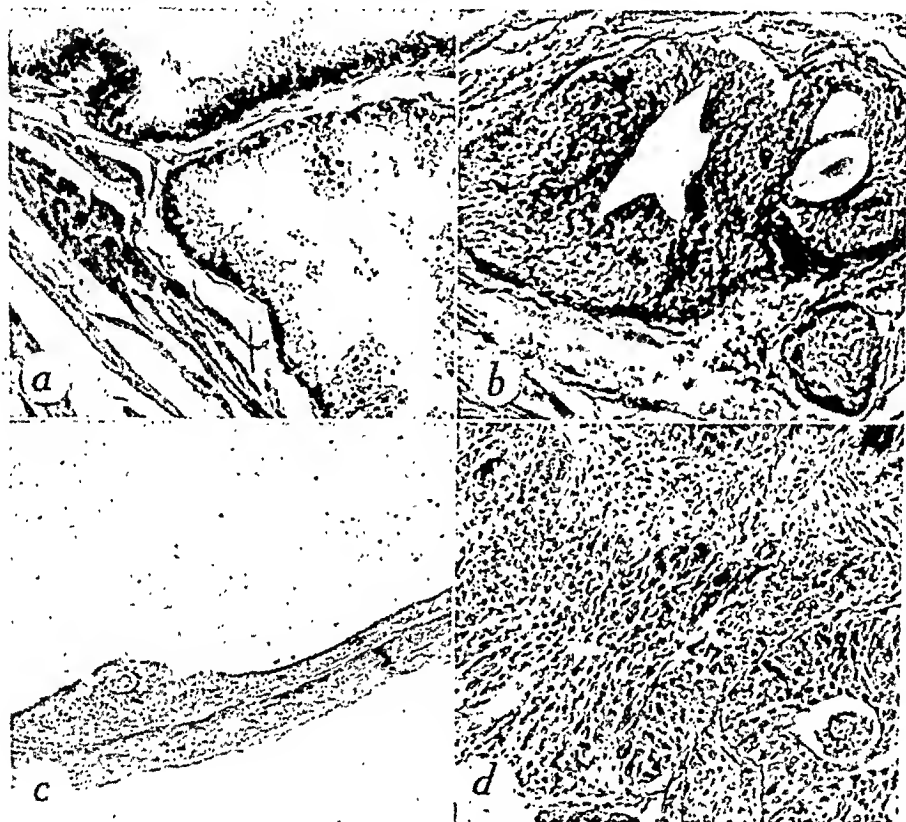


Fig. 7.—Ovarian dermoid cyst illustrating : *a*, Prostatelike tissue ($\times 100$). *b*, Brenner tumorlike structure ($\times 100$). *c*, Graafian follicle with ovum found in the wall of the cyst, which had grossly destroyed the entire ovary ($\times 23$). *d*, Squamous-cell carcinoma, grade 3 ($\times 75$).

Entodermal structures were noted in 71 per cent. Tissue resembling epithelium of the gastrointestinal tract was present in 12 per cent (Fig. 5, *b*). Salivary glandular tissue was seen in 16 per cent (Fig. 5, *c*) and was usually of the mixed mucous and serous type. Fetal lung tissue appeared in one case and adult lung tissue was identified in two instances (Fig. 5, *d*). Bronchial epithelium (Fig. 6, *a*) was present in 53 per cent, and bronchial glands were associated with this in 24 per cent. Cartilage was frequently found nearby and occasionally thyroid tissue was present in this same area. Thyroid tissue has been identified in 13 per cent. In four of these cases there was evidence of parenchymatous hypertrophy (Fig. 6, *b*) but in the two cases in which basal metabolic estimations had been made, the rate was within normal limits.

In one tumor, tissue resembling the prostate was found (Fig. 7, *a*).

In one section, tissue resembling the epithelium of the Brenner type of tumor was present. This was the only area of this nature in the cyst wall and the only case known in which cells of this type have been identified in a dermoid cyst of the ovary (Fig. 7, b).

An area of tissue resembling pancreas was seen in one section.

Islands of fatty tissue were found in 75 per cent of the tumors.

Evidence of irritation or infection was observed in more than half of the dermoid cysts. Lymphocytes were found in 51 per cent of the tumors. In 55 per cent, pseudoxanthoma cells were evident. In 61 per cent of the neoplasms, giant cells of the foreign body type were present, usually just beneath the stratified squamous epithelium (Fig. 1, b) or in the granulation tissue lining denuded areas.

The outer portions of the cyst walls were composed mainly of fibrous tissue, which, however, contained identifiable remnants of ovarian cortical tissue in 91 per cent. Unruptured follicles (Fig. 7, c) and corpora lutea were present in the great majority of cases, although the pathologist or surgeon frequently reported that the ovary had been completely destroyed. It should be remembered that in the literature pregnancy had occurred in connection with bilateral ovarian dermoids in more than fifty cases.¹

Clinical Characteristics.—To determine whether or not dermoid cysts of the ovary produce symptoms of diagnostic significance, Table VII was prepared to show the incidence and duration of the primary complaint. Pain was the most common complaint which brought the patient to seek medical advice. This pain varied from a dull ache to the sharp pain produced by torsion of the pedicle. The pain was referred to the side from which the tumor arose in all but two cases, and the duration varied from a few hours to twenty years. Five patients were admitted for "gallbladder colic" and were operated on primarily because of cholecystitis with or without cholelithiasis. One patient had a "ruptured" appendix, and two were suffering from pain of acute duodenal ulcers. One patient was found to have a concomitant tubal pregnancy.

Only thirty-four patients had noted any increase in the size of the abdomen, although the size of the tumor was as great in many patients who had not been aware of the presence of any abdominal swelling as in those who had noticed an increase.

One might expect multiple abnormalities of the menstrual flow but, as is shown in Table VIII, the menses were seldom affected and in almost all cases in which the menses were affected there were other pathologic lesions which would better explain the abnormal bleeding from the uterus. The age of onset of menstruation of fifty-four patients whose history contained this information is shown in Table IX. Table X shows the age of cessation of menstruation in forty-seven cases. It appears that altered physiology of menstruation is not a characteristic symptom of dermoid cysts of the ovary.

It has been stated that single and nulliparous adults are more susceptible to dermoid growths than women who have borne children. In this series, this is not true. Twenty per cent of this group were single. Of the 180 married women, only 11.7 per cent had not borne children at the time of operation. Of

TABLE VII. INCIDENCE AND DURATION OF PRIMARY COMPLAINT

COMPLAINT	DURATION OF COMPLAINT													INCIDENCE
	1 DAY	1 WEEK	1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS	1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS	10 YEARS	20 YEARS	
Pain														DURATION NOT RECORDED
Right lower quadrant of abdomen	1	1	3	4	1	1	3	1	3		1	10		
Left lower quadrant of abdomen	1	1	1	3	1	3						1	1	
Both lower quadrants of abdomen	1	1	1	1	2						1	1		
Backache					1			1						
Down legs														
Epigastric (duodenal ulcer)									1			1		
Right upper quadrant (gall-bladder colic)			1	2	3	7	9	6	4	1		1		
Abdominal enlargement			1	1		1								
Interfered with delivery			1	1		1	2	2	1	1				
Frequency of urination			1		1									
Urgency						1	1	3	1		3	1		2
Dragging sensation in pelvis				1		1	1	3						
Menorrhagia due to fibroids				1		1	1	1	1					
Menorrhagia and metrorrhagia due to fibroids			2	1		1	1	1						
Due to carcinoma of fundus					1				2					
Leucorrhœa												1	1	
Constipation											2		1	
Diarrhœa											1			
Sterility														
Lump in breast														
Fatigue, increasing exhaustion		1	1											
Enlarged thyroid			1			1					1	2		
No complaints. Cyst discovered at general examination						2		2					2	

these, one was married at the age of 45 years and another later became pregnant, which actually corrects the sterility percentage to 10.6. This is not in excess of the accepted incidence of sterility of married couples in the United States. The association of pregnancy with bilateral ovarian dermoids has been mentioned in the foregoing.

TABLE VIII. INCIDENCE OF MENSTRUAL HISTORY

MENSTRUAL HISTORY	CASES	PER CENT
Normal and regular	183	81.3
Normal but irregular	6	2.7
Menorrhagia (uterine fibroids present)	23	10.2
Menorrhagia (no associated lesion)	2	0.9
Metrorrhagia (uterine fibroids present)	4	1.8
Postmenopausal bleeding (carcinoma of fundus)	4	1.8
Inadequate menstrual history	3	1.3

TABLE IX. AGE OF ONSET OF MENSTRUAL PERIODS

AGE (YEARS)	CASES
11	5
12	16
13	16
14	10
15	4
16	2
17	1

Average age of onset = 13 years.

TABLE X. AGE OF CESSATION OF MENSES

AGE (YEARS)	CASES
38	1
40	1
41	2
43	2
44	1
45	5
46	3
47	1
48	4
49	2
50	13
51	3
52	2
53	3
54	1
55	2
56	1

Average age = 48.4 years.

A "sense of pressure" was the symptom responsible for 24 patients applying for medical aid. Of these, 10 had noted frequency of urination and 13 had felt a dragging sensation in the pelvis for from two months to ten years.

Abnormal vaginal discharge was complained of by three of the women, and in two of these, *Trichomonas vaginalis* was present and responded to local therapy. The third was found to have a draining tract direct from the dermoid into the vagina.

Six of the patients were registered because of a lump in their breasts which had been noted for from one week to one year. Seven complained of increasing exhaustion and five came to the clinic because of an enlarged thyroid gland.

Five patients complained of diarrhea of from six months' to five years' duration. Of these, three had carcinoma of the rectum or sigmoid.

Dermoid cysts were found in the ovaries of 57 women during the course of a routine general physical examination. These patients were in good health with no symptoms. They had applied for examination because of routine reasons involving insurance and so forth.

Table XI demonstrates that the size of the tumor was not necessarily related to the symptoms produced. As would be expected, those tumors producing abdominal enlargement and pressure were large, but equally large tumors did not necessarily produce symptoms in other cases. In two cases, delivery was complicated by dermoids measuring 8 cm. and 9 cm. in diameter, and in both cases mechanical difficulty was encountered. One patient required manual displacement of the tumor to allow the head to engage. The other required cesarean section.

TABLE XII. INCIDENCE OF COMPLICATIONS

COMPLICATIONS	CASES	PER CENT
<i>Preoperative</i>		
Twisted pedicle	17	7.6
Ruptured cyst	1	0.4
Parasitic cyst	2	0.9
Adhesions	12	5.3
Infected cyst	1	0.4
Vaginal fistula	1	0.4
<i>Operative</i>		
Cyst ruptured during removal	8	3.6
<i>Postoperative</i>		
Parotitis	1	0.4
Thrombophlebitis	1	0.4
Death	4	1.8
Peritonitis	1	0.4
Pulmonary embolism	2	0.9
Decerebrate rigidity (36 hr. postop.)	1	0.4

The complications met with in this series of dermoids are listed in Table XII. Preoperative complications existed in 15 per cent. In seventeen cases the pedicle of the cyst had become twisted. In these, pain, the predominating symptom, was sharp and agonizing and was referred to the side from which the tumor originated. One cyst had ruptured eight days before the patient's admission, but the patient recovered after a stormy convalescence. One cyst had ruptured into the vagina, through which it drained, but this patient died of generalized peritonitis.

Two of the dermoids had become detached from the ovary. One had attached itself to the parietal peritoneum of the abdominal wall and the other had become attached to the uterosacral ligaments.

Only one cyst was acutely infected, although it is generally agreed that these cysts are especially liable to such a complication.

The cyst was densely adherent in twelve cases, and in eight of these it ruptured during surgical removal. In none of these cases, however, did symptoms of peritonitis develop.

The mortality rate for the entire series was 1.8 per cent. Two women expired from pulmonary emboli and one died thirty-six hours postoperatively with decerebrate rigidity. In one case right parotitis and in another thrombophlebitis developed but both patients recovered satisfactorily.

Malignant transformation, an infrequent complication of dermoid cysts of the ovary (Figs. 7, *d* and 8), was present in three cases. In two of these the type was squamous-cell epithelioma, and in the third the neoplasm was an argentaffin carcinoma (carcinoid).

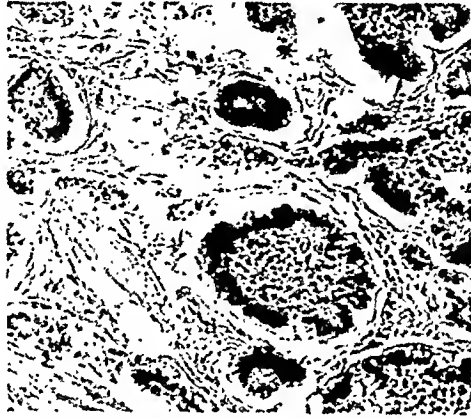


Fig. 8.—Grade 1 adenocarcinoma (carcinoid tumor) in wall of an ovarian dermoid cyst (X100).

In this series of tumors, the most frequent indication for surgical intervention was the tumor mass of the dermoid cyst. Next in frequency was the presence of uterine fibroids (Table XIII). This does not imply that the preoperative diagnosis was correct in these cases but merely the nature of the mass for which operation was recommended. The most frequent preoperative diagnosis (Table XIV) was ovarian cyst, but in 24 instances the correct diagnosis of ovarian dermoid was made. Of these 24, 12 were discovered or confirmed by the roentgenologist while examining roentgenograms of the kidney, bowel, or pelvis. The greatest single factor in roentgenologic diagnosis of dermoid cysts is the presence of teeth, since areas of calcification also occur in cases of calcified fibroids, ureteral and vesical calculi, phleboliths, and healed tuberculosis with calcification. Robins and White²⁴ have reported an additional aid to diagnosis in the absence of formed calcified shadows. They called attention to a rounded or ovoid mass, of decreased density due to the nature of the contents, and encircled by a well-defined ring of increased density produced by the capsule of the cyst. The area of decreased density is banded or mottled, an appearance which is explained by the hair mixed with sebaceous material. The recognition of these signs should increase appreciably the percentage of correct preoperative diagnoses.

As is evident in Table XV, there is a high incidence of associated lesions. Uterine fibroids are present in approximately a third of the cases. The significance of this association is not yet apparent.

Comment

From the microscopic findings in this series of 100 dermoid cysts of the ovary, ectodermal derivatives were found to be present in 100 per cent of the

TABLE XIII. INDICATIONS FOR SURGICAL INTERVENTION

INDICATION	CASES
Dermoid cyst	162
Pseudomucinous cyst	8
Simple cyst	3
Serous cyst adenoma	3
Tarry cyst	2
Parovarian cyst	1
Endometriosis	1
Ruptured appendix	1
Uterine fibroids	20
Cholecystitis	7
Carcinoma of fundus of uterus	6
Carcinoma of rectosigmoid	3
Carcinoma of ovary	2
Pelvic inflammatory disease	4
Tubo-ovarian abscess	1
Ectopic pregnancy	1

TABLE XIV. PREOPERATIVE DIAGNOSIS OF PELVIC MASS

DIAGNOSIS	CASES
Ovarian cyst	86
Uterine fibroids	32
Ovarian dermoid	24
Ovarian mass	17
Cyst anterior to uterus	4
Cyst posterior to uterus	10
Adnexal tumor	5
Pelvic mass	19
Pelvoabdominal tumor	10

TABLE XV. INCIDENCE OF ASSOCIATED LESIONS

LESION	CASES
Uterine fibroids	70
Chronic appendicitis	39
Acute appendicitis	1
Cyst of Morgagni	23
Pseudomucinous cystadenoma	11
Serous cystadenoma	4
Simple ovarian cyst	11
Tarry cyst	4
Fibroma of ovary	2
Adenocarcinoma of ovary	4
Adenocarcinoma of uterus	6
Fibrosarcoma of uterus	1
Carcinoma of rectosigmoid	5
Cholecystitis	10
Hydrosalpinx	8
Pelvic inflammatory disease	6
Duodenal ulcer	2
Endometriosis	3
Tuberculous perisalpingitis	2
Adenomyoma	1
Ectopic pregnancy	1
Bicornate uterus	1
Unicornate uterus	1

tumors, mesodermal derivatives in 93 per cent, and entodermal derivatives in 71 per cent.

The percentage of both mesodermal and entodermal structures present was greater than those reported by other investigators. This is no doubt due to the fact that multiple sections (ten to fifteen) were taken from each dermoid cyst rather than the one or two usually studied. Also, sections were always taken through the dermoid process even if it contained bone. Derivatives of all three germ layers are more likely to be found in this protuberance than elsewhere in the cyst. It is very probable that if serial sections were taken of each tumor, the incidence of mesodermal and entodermal structures might more nearly approach 100 per cent.

The term "dermoid cyst," which describes only one portion of the cyst, does not fully define nor describe the growth. The same name is applied, and correctly so, to the sequestration dermoids of the skin and other parts of the body, which contained structures derived only from the ectoderm. Since all embryonic layers may be represented, these cysts of the ovary should be regarded as teratomas and should be designated as cystic teratomas to distinguish them from the solid teratomas of the ovary.

None of the suggested hypotheses appear to explain adequately the histogenesis of these tumors, but, regardless of their intimate cause, it is probable that the tumor tissue was formed long before it was discovered. These cysts are lined with skinlike epithelium containing sebaceous glands, which no doubt form the contents of the cyst. The activity of the sebaceous glands is greatly augmented at puberty. The finding of these tumors during the reproductive life of the individual may well result from the active secretion from the glands lining the wall of the cyst. The increased incidence after puberty may be due to the more rapid distention of the cyst cavity as a result of stimulation of the sebaceous glands at this period of the patient's life.

These tumors occurred in all decades of life but they are most commonly found during the period of sexual activity. The oldest patient in our series was 72 years of age and she was of the opinion that the cyst had bothered her for more than twenty years. The size of the cysts apparently was not related to the age of the patient. The rate of growth was slow. It is not unlikely that many women live a normal lifetime with undiscovered teratomas.

It has been claimed that these cysts have a predilection for one side or the other, but in this series they occurred almost equally on either side.

It has been stated, "Dermoids are rarely lined with skin. This structure is confined to the embryonal rudiment or to its immediate neighborhood." This we found to be untrue. In fact, it was common to encounter stratified squamous epithelium, sebaceous glands, and hair follicles in all portions of the cyst walls, even in that portion farthest from the focus.

It has been the opinion of some that single and nulliparous adults are more susceptible to these cystic tumors than women who have borne children, but in this study only 20 per cent of the patients were unmarried. Of the married patients, only 11.7 per cent had not borne children at the time of operation. Of these, one had not married until the age of 45 years and one has since been de-

livered of a full-term child. This corrects the infertility rate to 10.6 per cent. It is generally accepted that 10 per cent of the marriages in the United States are barren. Reproductive function is therefore affected slightly, if at all, by the presence of these tumors.

There were no characteristic symptoms of cystic teratomas. Menstrual disturbances when present were usually the result of associated pathologic lesions. The larger the neoplasm, the more likelihood there was of the presence of clinical manifestations, as in any ovarian tumor.

When complications occurred, such as torsion of the pedicle or rupture of the cyst, the diagnosis of "a surgical lesion" became apparent but the exact type of the "ovarian pathology" was not diagnosed with any degree of certainty preoperatively. The contents of the cyst have been considered very irritating to the peritoneum. Yet, one cyst ruptured preoperatively and eight ruptured during surgical removal without producing any symptoms of peritonitis. This is probably explained by the fact the ruptured contents were washed from the abdominal cavity with physiologic saline solution at the time of operation. One dermoid ruptured into the vagina and produced fatal peritonitis. Peritoneal "implants" may take the form of numerous cellular nodules associated with a foreign body giant-cell reaction, but, in this group of cases, only one cyst had ruptured into the peritoneal cavity preoperatively and no implants were evident.

In two cases the cyst interfered with the progress of labor. Large myomas of the uterus are more adaptable than ovarian cysts to the enlarging fetus, and the experience gained from management of a pregnancy in a myomatous uterus is not applicable to the complicating presence of ovarian tumors. Ovarian cysts are more prone to produce dystocia or to rupture during delivery and produce fatal peritonitis. If the tumor is large and in position to obstruct pelvic delivery, it is imperative that surgical intervention be considered during the pregnancy.

The only satisfactory treatment of cystic teratomas of the ovary is surgical removal. Inasmuch as this study revealed that 91 per cent are associated with ovarian tissue, it is especially recommended that when possible the neoplasm should be resected from the normal ovarian tissue. This is especially desirable if the tumor is bilateral. The practice of tapping an ovarian cyst fortunately has been discarded. In reading the reports in the literature of a century or more ago, one is impressed by the number of deaths following the tapping of ovarian cysts "containing hair and oily material." That malignant lesions do occur, even though in a small percentage of cases, is an additional reason for early surgical removal. It also is a good argument for the routine microscopic examination of all tumors even though they appear grossly to be benign.

Conclusions

Study of the data obtained from the records of 225 patients who had cystic teratomas removed surgically at the Mayo Clinic and from the microscopic examination of 100 consecutive tumors permits of drawing the following conclusions:

Ectodermal derivatives were present in 100 per cent of the tumors, mesodermal structures in 93 per cent, and entodermal derivatives in 71 per cent of these cysts.

The high percentage of mesodermal and entodermal elements was due to the fact that multiple sections have been examined microscopically. Serial sections would probably have revealed more.

The term "dermoid" is inaccurate and should be replaced by the term "cystic teratoma."

The hypotheses that have been advanced to explain the histogenesis of these neoplasms do not explain their origin adequately.

These tumors occurred with equal frequency in either ovary.

Twelve and four-tenths per cent were bilateral.

The average diameter was 8.2 cm.

The incidence of cystic teratomas was 5 per cent of all ovarian neoplasms.

Malignant lesions occurred in 3 per cent of cystic teratomas.

Symptoms associated with these cysts had no differential diagnostic value.

Surgical removal was the treatment of choice, but, when possible, resection of the tumor was done to conserve ovarian function.

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THE OBSTETRICIAN'S RESPONSIBILITY FOR THE HAZARDS OF THE FIRST FEW DAYS OF LIFE WITH SPECIAL REFERENCE TO ANOXIA AND PREMATURETY*

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THE obstetrician's responsibility with regard to the hazards of the first few days of life are many and varied. Consideration of all of the factors which might lead to a reduction of these hazards would include almost the entire field of obstetrics and would lead to much controversy. Instead of attempting to cover such a wide field, I have reviewed the last five years' records of the deliveries of all infants who reached the period of viability, with the view to ascertaining for this presentation how we might lower our infant mortality at the Long Island College Hospital.

Maternal and Infant Mortality

In the five-year period from 1940 through 1944, 7,580 infants weighing 1,000 grams or over were born at the Long Island College Hospital. Twelve, or 1 in 631, of the mothers died. (There were three additional maternal deaths which are not included in these statistics because they occurred in the middle of pregnancy long before the stage of viability had been reached.) During this period, 99, or 1.3 per cent, of the infants were born dead and 101, or 1.33 per cent, died while in the hospital. The total number of stillbirths and neonatal deaths accordingly was 200, a combined fetal and neonatal mortality of 2.63 per cent. The statistics for each of these five years are shown in Table I.

TABLE I. MATERNAL AND FETAL MORTALITY
PREMATURE (1,000 TO 2,500 GRAMS) AND FULL-TERM DELIVERIES
(LONG ISLAND COLLEGE HOSPITAL)

	DELIVERIES OVER 1,000 GRAMS	MATERNAL DEATHS	STILL- BIRTHS	NEONATAL DEATHS	FETAL AND INFANT DEATHS	FETAL AND NEONATAL MORTALITY (%)
1940	1381	2	19	19	38	2.75
1941	1537	1	21	17	38	2.47
1942	1651	3	18	23	41	2.48
1943	1583	4	23	23	46	2.90
1944	1428	2	18	19	37	2.51
	7580	12*	99	101	200	2.63
		or (1 in 631)	or 1.3%	or 1.33%		

This combined infant mortality of 2.63 per cent is lower than that which is reported from some institutions. Four important factors may be responsible for our better results. One of these is the physical setup of our nurseries, which made possible the use of the unit

*Read at a meeting of the Brooklyn Gynecological Society, April 6, 1945.

system in caring for newborn infants. This, together with a separate formula room in which an aseptic technique similar to that followed in the surgical operating room is employed, has greatly reduced the incidence of infection. The second factor is the excellent cooperation which we receive from the pediatric department. While the attending obstetrician nominally is responsible for the child which he delivers, its care is turned over to the department of pediatrics as soon as it leaves the delivery room. The third factor is the fact that we discuss all stillbirths and neonatal deaths at our monthly staff meetings, and the pediatric resident participates in this discussion. The fourth factor is our reluctance to push sedation beyond the point at which it is safe for the child. A number of years ago, when we were using morphine and scopolomine according to the so-called "twilight sleep" technique, we learned that sedative drugs given to the mother might cause the loss of the child. While we knew nothing about anoxia in those days, our experience made us cautious. As a result, we do not promise our patients an absolutely painless labor, but we aim to relieve as much pain as is possible within the limits of safety for the child.

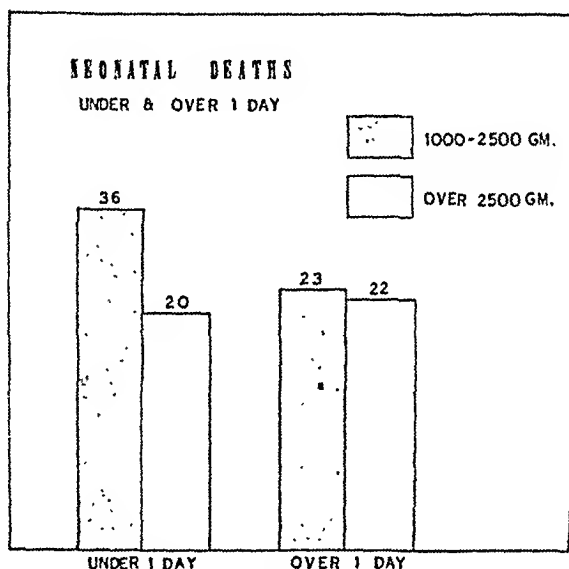


Fig. 1.

Causes of Neonatal Deaths

The effect of detrimental prenatal influences and serious intrapartum injuries is clearly demonstrated by the fact that 36 of the 59 premature and 20 of the 42 full-term neonatal deaths occurred within twenty-four hours after birth (Fig. 1). The responsibility for nearly 60 per cent of the neonatal deaths, therefore, rests almost entirely upon the obstetrician. In addition, the obstetrician must accept a fairly large share of the responsibility for the neonatal deaths which occur after the first day, if our experience may be taken as a criterion. That this is so is evident from a grouping of the 101 neonatal deaths according to their causes. Congenital anomalies were responsible for 32.6 per cent of all deaths. Nine and nine-tenths per cent were due to infection. Brain hemorrhage was demonstrated in 14.8 per cent, while the remainder, or 41.5 per cent, showed nothing more than congenital atelectasis when autopsy was permitted (Fig. 2). In the latter group, however, respiratory symptoms were almost invariably present, and most of the deaths in this classification were preceded by periods of intermittent cyanosis. Because this is the largest of the four groups, and because 50 per cent or more of the infants in each group weighed between 1,000 and 2,500 grams, any future improvement which may be obtained in our service must come largely from a lessening of the hazards which accompany premature deliveries, or from a reduction of this large group of cases which are included under the heading of intermittent cyanosis.

Effect of Anoxia

Because the large group which has been included under the heading of intermittent cyanosis showed the same respiratory symptoms which are present when tentorial tears and

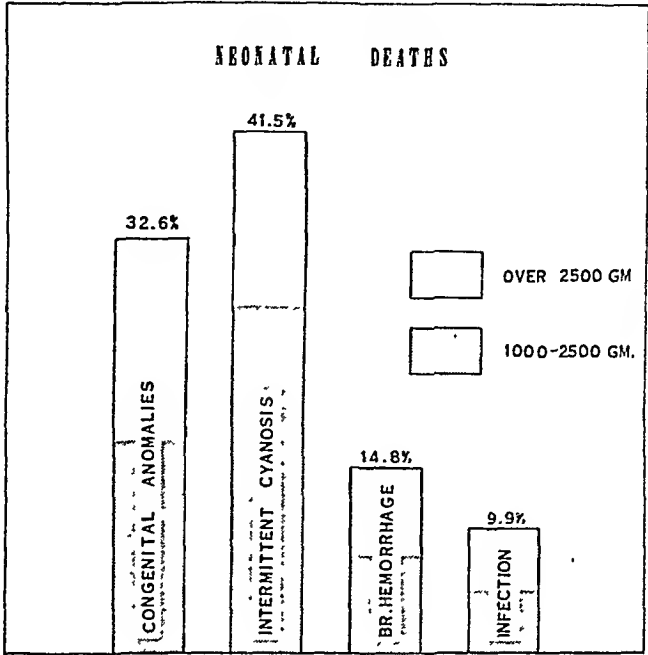


Fig. 2.

OXYGEN SATURATION OF THE BLOOD
GOING TO AND COMING FROM THE PREGNANT UTERUS

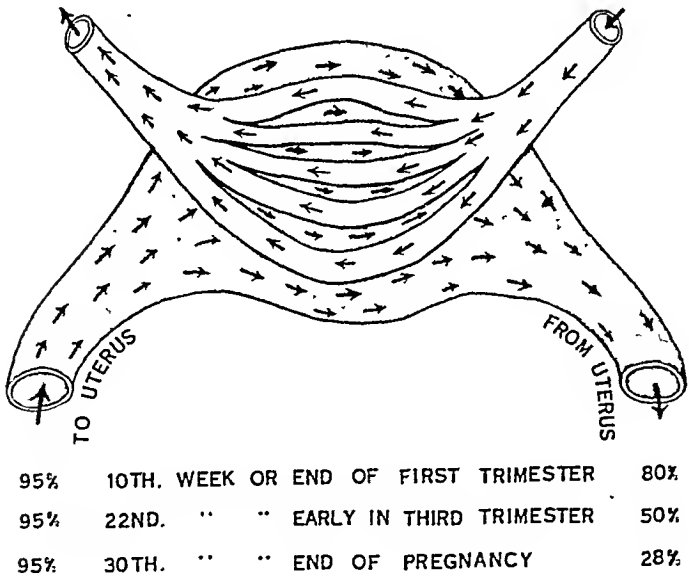


Fig. 3.

injuries of the brain are demonstrable at autopsy, it is our impression that most of the cases in this large group included under the heading of intermittent cyanosis have congenital atelec-tasis and show respiratory symptoms, because the brain likewise has been injured. Although

the lesion cannot be demonstrated by our present methods, it quite probably is produced by the effect of anoxia on the cells of this vital structure. If this hypothesis is correct, a review of some of the causes of anoxia may be of service. We all are familiar with the effect of prolapse of the cord, of knots in the cord and of coils of cord about the neck and extremities. We also know that the cord may be compressed and the circulation cut off when the uterus becomes molded about the child in a long dry labor. Because such complications and their treatment are familiar to all obstetricians, their discussion will be omitted. Other and more common causes of anoxia may not be so familiar to the average obstetrician. To understand them, one must study the mechanism by which oxygen and carbon dioxide are exchanged between the fetal and maternal circulations at the placental site. A crude diagram of the fetal and maternal circulations is shown in Fig. 3. The unshaded portion of this diagram represents the fetal circulation. Fetal blood enters the placenta from the umbilical arteries, then passes through the capillary systems of the chorionic villi and is returned to the fetus by way of the umbilical vein. The shaded portion represents the maternal circulation. Maternal blood from the uterine and ovarian arteries passes through an arteriovenous fistula, the placental lake, to the maternal venous circulation. If the circulation in the human is similar to that of the rabbit, the fetal blood flows in a direction opposite to that of the maternal blood stream.¹ In the rabbit at the tenth week, or the stage corresponding to the end of the first trimester in the human being, the arterial blood which enters the placental site through the maternal circulation is 95 per cent saturated with oxygen. When it leaves the uterus at this time, it is 80 per cent saturated. As gestation advances, and the fetus requires more oxygen, the saturation of the blood which comes from the placental site is diminished until, at the thirtieth week or the end of pregnancy, the blood which comes from the pregnant uterus is only 28 per cent saturated.² This experiment shows that the transmission of oxygen by the maternal blood through the placental site does not increase in proportion to the increasing demands of the developing fetus. If it could have been prolonged, and if the oxygen saturation of the blood which comes from the uterus continued to diminish at a similar rate, one might conclude that within a short time after term the oxygen supply would have been inadequate for the survival of the fetus. The relative inadequacy of the placental lake as a source of oxygen when compared with the lungs after birth is also shown by the fact that the red blood count, the hemoglobin, and the volume of the red blood cells are greater at birth than they are several weeks later. The apparent inability of the maternal blood to furnish an adequate supply of oxygen is thus compensated for, to some extent, by an increase in the fetal blood's ability to absorb oxygen, the oxygen capacity of fetal blood being 20.8 volume per cent as compared with an oxygen capacity of 15.4 volume per cent for maternal blood.³ These blood findings at birth have led to the suggestion that the fetus is subjected to the same difficulty in securing an adequate supply of oxygen as is experienced by an adult man who lives in the rarified atmosphere of a very high mountain.

If the oxygen saturation of the maternal blood which flows through the placental lake normally is so inadequate that the fetus must make compensatory adjustments in its own blood to secure an adequate supply of this essential element, it must be evident that anything which might reduce the oxygen content of the maternal blood, or which might retard the circulation of that blood through the placental lake might very well lead to anoxia in the fetus.

A large maternal hemorrhage might so reduce the oxygen carriers in the mother's blood as to cause asphyxiation of the fetus in utero. This explains the sudden death of the fetus which often follows the removal of a large amount of blood when a massive phlebotomy is done for eclampsia. It also explains the frequent death of the fetus in those cases of placenta previa which are accompanied by profuse hemorrhage. In the interest of the child, accordingly, phlebotomy is contraindicated in eclampsia, and such cases of placenta previa should, if possible, receive a blood transfusion before pregnancy is interrupted and the fetus is subjected to a further diminution of its oxygen supply. The use of oxygen and transfusion immediately after birth also may prove of benefit to the child.

A knowledge of the difficulties under which the fetus obtains its oxygen also shows why the fetus so frequently dies in utero when the mother is suffering from the marked dyspnea

which accompanies pneumonia and cardiac failure. It also leads to the suggestion that some of these fetuses might be saved by more frequent use of oxygen in the treatment of pneumonia as well as in the treatment of decompensation in cardiac disease. For the same reason, termination of the labor in these cases by low forceps and episiotomy under local anesthesia, may be a lifesaving measure from the fetal as well as the maternal standpoint.

When the mother's respirations are slowed and made more shallow by the use of sedative drugs and anesthetics, the oxygen supply to the placental lake is diminished, and the danger of intrauterine anoxia and asphyxiation are increased to such an extent that most of the methods which have been recommended for the relief of pain during labor may cause the death of the child if they are not given with caution. These drugs also pass through the placenta and depress the respiratory center of the fetus, with the result that respiration after birth often is impaired and further anoxia is thus produced. While artificial respiration may sustain life until the respiratory center has recovered from the action of these drugs and the child is able to breathe naturally, the effect of the anoxia on other parts of the brain may lead to serious consequences.

Even though the maternal blood may contain an adequate supply of oxygen, alterations in the pressure head at the placental site may prevent the fetus from obtaining its full requirements. During a uterine contraction, the pressure head which may be adequate in systole is quite inadequate during diastole.⁴ When the uterus contracts in labor accordingly, the oxygen supply to the fetus is greatly diminished, and manifestation of this diminution is revealed by changes in the rate and rhythm of fetal heart sounds. When the contractions are intense, or when they are prolonged, the difficulty is increased. This explains the frequent occurrence of stillbirths in precipitate labor, and also shows how posterior pituitary extract, when used during labor, causes the death of the child. These observations should lead us to attempt to diminish the violence of uterine contractions with small amounts of an anesthetic in cases of precipitate labor. They also indicate that posterior pituitary extract either should not be used, or should be used with great caution, during labor.

When in the course of labor, changes in the rate and rhythm of the fetal heart sounds indicate that the fetus is embarrassed, its oxygen supply may sometimes be increased by giving oxygen to the mother. The use of an anesthetic to diminish the intensity of the uterine contractions may also aid in this connection. If these measures fail, immediate delivery is indicated whenever the labor has progressed sufficiently far to warrant operative interference. If, as has been stated, in the large proportion of infants whose deaths were preceded by intermittent cyanosis and whose autopsies revealed nothing but congenital atelectasis, the real cause of death was a brain lesion caused by anoxia, appreciation of the physiologic principles outlined should lead the obstetrician to apply all of the measures which have been suggested to prevent and relieve anoxia. Appreciation of these principles also should direct the pediatrician's attention toward the advisability of prolonging the use of oxygen after respiration has been established, whenever anoxia is observed. If the pediatrician also is mindful of the fact that all respiratory stimulants do more harm than good, when the supply of oxygen is inadequate to support the metabolism of the brain cells, he will be very cautious in the use of such stimulants in the presence of anoxia.⁵

Effects of Prematurity

In addition to the cases which I have included under the heading of intermittent cyanosis, the premature deliveries contributed very materially to our infant mortality. Of the 200 stillbirths and neonatal deaths, 90 weighed between 1,000 and 2,500 grams. While less than a third of the stillbirths were in this class, prematures comprised almost 60 per cent of the neonatal deaths (Fig. 4).

As has been observed many times, the mortality of these underweight infants diminishes as the weight increases. Forty-six and six-tenths per cent of our cases in the 1,000- to 1,500-gram group were lost, while only 20.8 per cent of those weighing 1,500 to 2,000 grams, and 5.4 per cent of those in the 2,000- to 2,500-gram group died. Our gross mortality for the entire series was 12.4 per cent. Comparison of the results obtained in our series of 473

cases with those recorded in New York City for the year 1939 is shown in Fig. 5. In all groups our results were somewhat better than those of the entire city. The greatest difference, however, is to be observed in the 1,000- to 1,500-gram cases.

In a previous paper, many of the ways in which the obstetrician may aid in reducing the mortality of prematures were discussed.⁶ The most important of these are as follows:

1. Adequate supervision of the hygiene of pregnancy.
2. Proper advice concerning diet, coitus, rest, and exercise.
3. Immediate notification of the obstetrician whenever any untoward symptoms appear.
4. Early discovery of presence of syphilis, and vigorous treatment of the same throughout pregnancy.
5. Prevention of congestive failure in cardiac cases by joint cardiologist and obstetrician supervision.
6. Determination of the size of the child by means of the x-ray, and consultation with another competent obstetrician before artificially interrupting pregnancy.
7. Elimination of morphine, scopolamine, barbiturates, and general anesthesia in all premature labors.

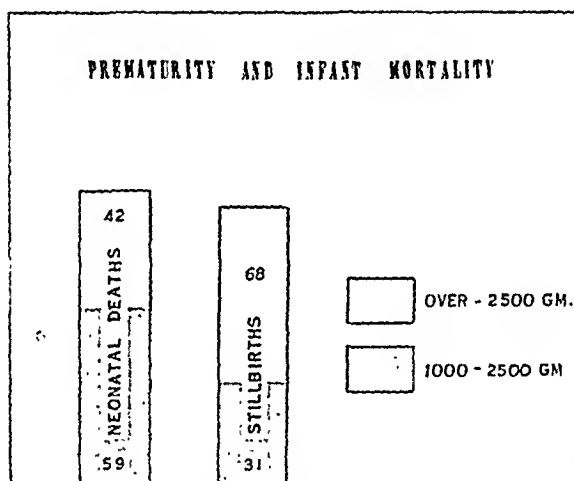


Fig. 4.

8. The administration of vitamin K to the mother before interrupting pregnancy and to all premature infants immediately after birth.⁷

9. Preservation of the membranes as long as possible and episiotomy to protect the premature infant from the pressure effects of labor.

10. Spontaneous delivery of the second twin and avoidance of version and extraction wherever possible.

11. Postponement of the tying of the cord until it stops pulsating in order that the child may receive as much blood from the placenta as possible.

12. Reception of the newly born premature infant in a tub of warm water to prevent chilling while waiting for the cord to stop pulsating.

While time will not permit a repetition of the discussion of all of these items, the effect of pressure on the brain of the premature infant and the effect of the various methods of delivery are sufficiently important to warrant further discussion of these significant items.

Pressure Effects

In the premature infant the blood vessel walls and the supporting structures of the brain are imperfectly developed. Not only are brain injury and intracranial hemorrhage more common in premature than in full-term infants, therefore, but the frequency and extent of the damage done, vary inversely with the duration of pregnancy. In other words, the smaller the fetus the greater will be the risk of brain damage during delivery. Although premature

births occurred only once in every 16 deliveries in our series, 50 per cent of all of the deaths which were due to brain injury were in prematurely born infants. Most of the danger is encountered in the second stage of labor and results from pressure of the soft and malleable head against the resisting pelvic floor. To prevent this type of brain injury and intracranial hemorrhage, the membranes should be preserved as long as possible and the second stage of labor should be terminated shortly after the head reaches the level of the ischial spines. The latter usually can be accomplished by doing an episiotomy under local anesthesia. Since this procedure removes most of the resistance at the outlet, it should be used in all cases. If the birth of the head does not follow soon after an episiotomy is done, extraction by low forceps is indicated.

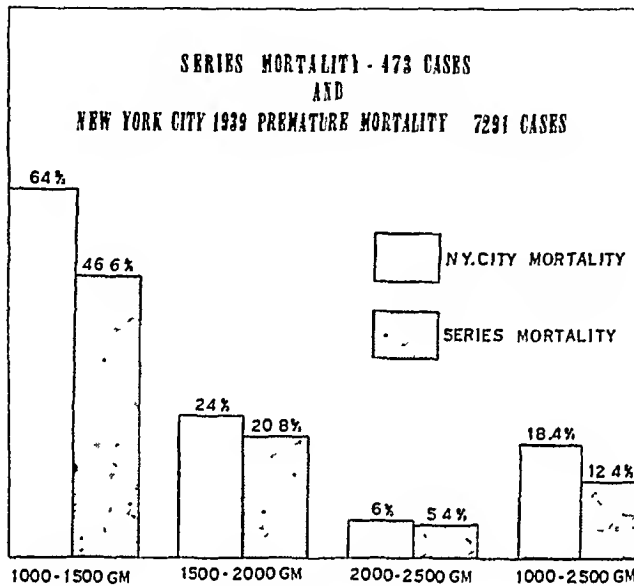


Fig. 5.

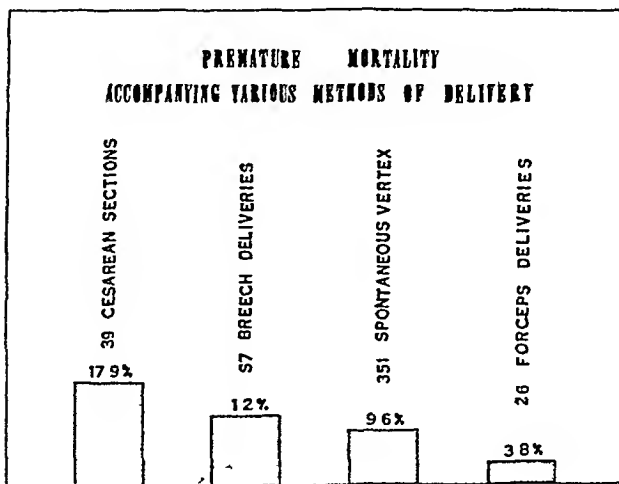


Fig. 6.

Effects of the Various Methods of Delivery

Fig. 6 is a graphic representation of the mortality of the various methods of delivery when the child is premature. This chart also illustrates how inaccurate statistics may be when they are compiled by a brainless tabulating and recording machine. According to these figures, forceps was the safest and cesarean section the most dangerous method of delivery, while breech deliveries were almost as safe as vertex. Careful study of the entire series, however, shows that these conclusions are erroneous.

Breech Deliveries

When the breech deliveries are broken down into the several 500-gram weight groups, it is noted that 70 per cent of the infants weighing 1,000 to 1,500 grams were lost, while the series mortality for this weight group was only 46.6 per cent. The mortality from breech

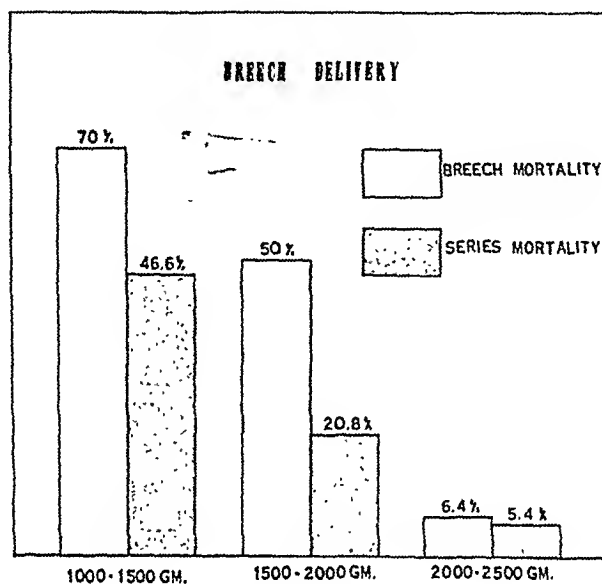


Fig. 7.

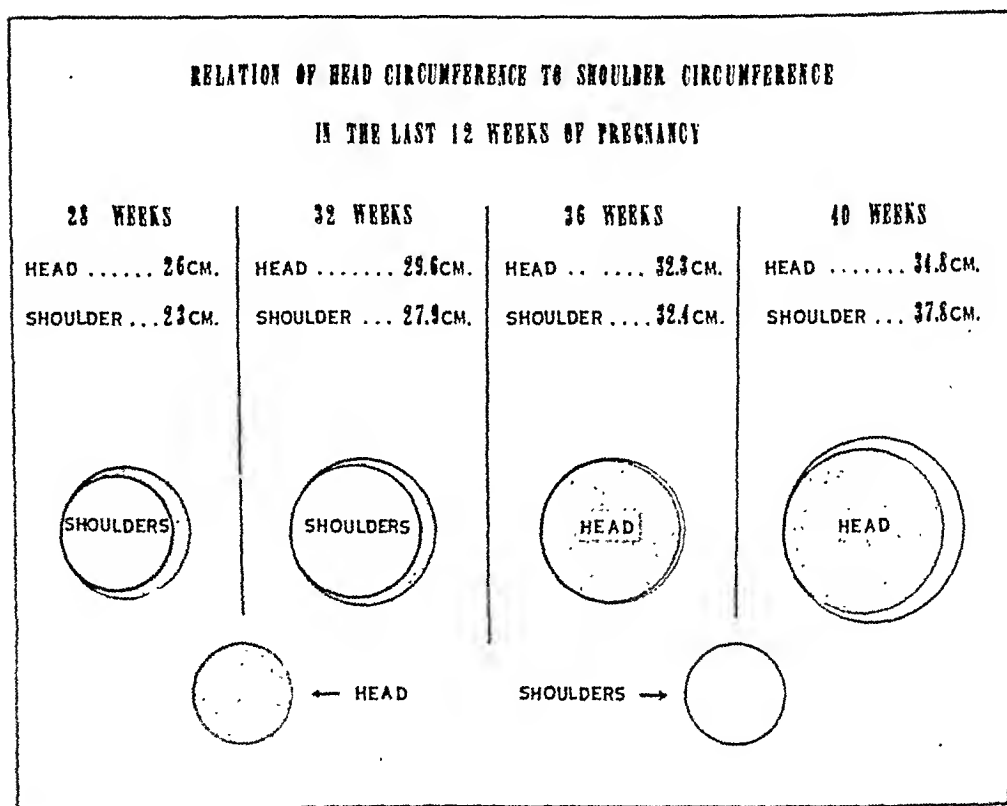


Fig. 8.

delivery of the infants weighing 1,500 to 2,000 grams was 50 per cent, or almost two and one-half times the mortality for the series infants of the same weight. It was only in the larger infants which weighed over 2,000 grams that the mortality of breech delivery approached

that of the series (Fig. 7). Instead of proving that breech delivery is almost as safe as vertex, this chart shows it to be an extremely dangerous method whenever the child is under 2,000 grams. The reason for the high death rate among these very small infants should be quite clear to all of us. Every obstetrician has observed that in the young prematures the circumference of the shoulders and body is less than the circumference of the fetal head. When the cervix is dilated sufficiently to permit the passage of the shoulders, therefore, it is not large enough for the head. The aftercoming head, accordingly, is caught by the cervix and the child either dies from asphyxia or from the injuries which are caused by the difficulties encountered in delivering the arrested aftercoming head. This point is well illustrated in Fig. 8. According to the measurements of Scanmon and Caulkins the circumference of the shoulders at the twenty-eighth week is 3 cm. less than the occipitofrontal circumference of the child's head. At 32 weeks, the girth of the shoulders is still less than that of the head. Four weeks later, the shoulder circumference equals or slightly exceeds the head circumference, and at term there is observed the normal relationship in which the shoulder circumference is considerably greater than that of the head. The shaded areas represent the head, and the unshaded, the shoulder circumferences. Although both the head and the shoulders increase in size as pregnancy advances, the rate of the shoulder increase exceeds that of the head, with the result that the shoulder girth equals the girth of the head at 36 weeks and exceeds it at term.

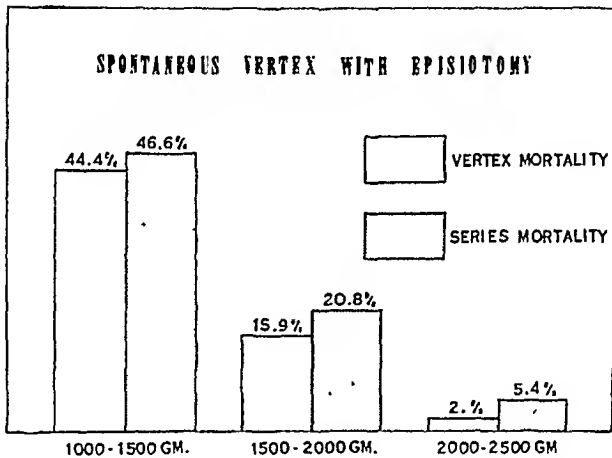


Fig. 9.

Vertex Deliveries

While 9.6 per cent of the 351 infants delivered as spontaneous vertex cases were lost, the mortality for the spontaneous vertex deliveries which were accompanied by episiotomy was lower than that of any other method of delivery. Although the death rate was only slightly below that of the series in the 1,000 to 1,500 gram cases, it was 20 per cent lower in the 1,500 to 2,000 gram group, and over 50 per cent lower than the series mortality in the infants weighing 2,000 to 2,500 grams (Fig. 9). The results in the 201 cases delivered in this manner are in accordance with our previous experience, which has shown spontaneous delivery with episiotomy under local anesthesia to be the safest method of delivery for the premature infant.

Cesarean Section

Thirty-nine cases were delivered by cesarean section with an infant mortality of 17.9 per cent. In three instances the child weighed only 1,000 grams and all three survived. The mortality in the 1,500 to 2,000 gram cases was slightly lower than the series mortality for the same weight group. A surprisingly high mortality of 20.8 per cent followed the use of cesarean section in the infants weighing from 2,000 to 2,500 grams (Fig. 10). This chart again shows the fallacy of drawing conclusions from plain figures without analyzing the circumstances of each case. Instead of showing a lowered mortality for the larger infants.

the mortality was considerably higher in this group. The reason for the poor results obtained by cesarean section was not due to the method of delivery, but was due either to the condition of the child, or to the maternal complication for which the cesarean section was done. Two of the 7 deaths were due to congenital anomalies, and in 3 instances in which the child was lost, the operation was done for placenta previa. Not only is the child subjected to intra-uterine anoxia in placenta previa, but, because of the mother's condition, the operation is done so rapidly that the ordinary technique which is followed when prematures are delivered by this method cannot be employed. If the 9 cases in which cesarean section was done for placenta previa and the 2 in which the child died as a result of congenital anomalies are deducted from the 39 cesarean sections, there remain 28 operations with 2 deaths, a premature infant mortality of 7 per cent. Cesarean section at times, accordingly, is a valuable method of delivery. It should be done under local anesthesia without preliminary sedation. The child should not be grasped by the feet and violently jerked out of the uterus. On the contrary, it should be delivered head first with as gentle manipulations as the circumstances will permit. If there is no bleeding from the placental site and usually there is none when the low technique is followed, the cord should not be severed immediately. While waiting for its circulation to take up some of the placental blood the child may be held by the feet so that whatever material is in the nasopharynx may drain away.

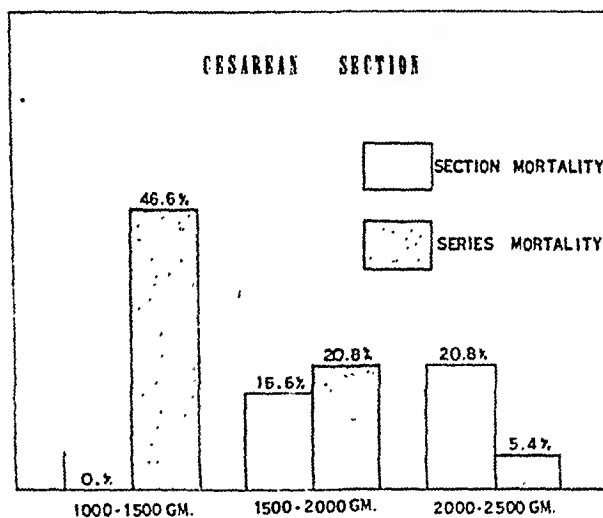


Fig. 10.

Summary

1. The annual maternal and infant mortality at the Long Island College Hospital is given for the five-year period from 1940 through 1944.
2. Anoxia and prematurity were the commonest causes of neonatal deaths.
3. The causes of anoxia and suggestions for its prevention and treatment are given.
4. The various measures which might reduce the incidence and mortality of premature births are outlined.
5. The cause and prevention of pressure effects on the head of the premature infant are discussed.
6. The results of the various methods of delivery of premature infants are compared.
7. Breech delivery is found to be most dangerous and the cause of the great danger of this method of delivery is emphasized.

8. Spontaneous vertex delivery accompanied by episiotomy under local anesthesia is the safest method of delivery for premature infants.

9. Cesarean section is not a dangerous but a valuable method of delivery. The high premature infant mortality which is recorded for this operation usually is due to the maternal or fetal complication which serves as the indication for the operation rather than to the method of delivery.

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STUDIES OF SURGICAL MORBIDITY*

II. Effect of Prostigmine on the Urinary Tract in Gynecologic Surgery

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URINARY tract infections are the most common complications following gynecologic surgery. In a previous study¹ the authors showed that 43 per cent of the identified morbid conditions in abdominal hysterectomies performed at St. Luke's Hospital were due to infections of the urinary tract. Residual urine, urinary retention, repeated catheterizations, and the symptoms resulting therefrom make a considerable problem for the gynecologist.

Gordon,² Marden and Williamson,⁴ and Trautenberg and Oliver,⁵ have reported the successful use of prostigmine methylsulfate for the relief and prevention of postoperative abdominal distention and urinary retention in abdominal and gynecologic surgery. It was thought that the "prophylactic" administration of prostigmine methylsulfate, as advocated by Gordon³ might prove of value in an attempt to control these postoperative complications.

The purpose of this study is to compare the effect of prostigmine methylsulfate† on the urinary tract of patients undergoing gynecologic surgery with a similar group undergoing the same type of surgery who did not receive the drug. The effect of prostigmine methylsulfate on postoperative abdominal "gas pains" was also studied.

Prostigmine methylsulfate may be described chemically as the dimethylcarbamate ester of 3-hydroxyphenyl-trimethyl-ammonium methylsulfate. It is hereafter referred to in this study as prostigmine.

Methods and Material

There were 170 patients in the series; 50 per cent (85) received prostigmine, and 50 per cent (85) did not receive any so-called "prophylactic treatment."

The series included private and service patients; the latter both Negro and white. They were operated upon by the five attending gynecologists and the resident on the gynecologic service. The following method was employed:

One ampule (1 c.c. of the 1:2,000) of prostigmine was given with the preoperative medication, and one ampule was given immediately on return from surgery. Following abdominal operations one ampule was given every six hours for forty-eight hours. Following vaginal operations one ampule was given every four hours for forty-eight hours. All doses were given intramuscularly.

For the sake of simplicity, the types of surgery were divided only into abdominal and vaginal procedures. Abdominal surgery included total and subtotal hysterectomy, salpingectomy, oophorectomy, and miscellaneous abdominal procedures. Vaginal surgery included vaginal hysterectomy and all forms of vaginal plastic operation, i.e., perineorrhaphy, trachelorrhaphy, colporrhaphy, vulvectomy, and combinations of these procedures.

*Presented before a meeting of the Chicago Gynecological Society, Dec. 15, 1944.

†The prostigmine methylsulfate used in this study was furnished by Hoffman-La Roche Company, Nutley, New Jersey.

Urinary Tract Morbidity

In order to be classified as having a urinary tract infection the patient had to have (1) clinical symptoms of dysuria and frequency, and/or urgency and burning on urination, and (2) laboratory findings of more than 20 mg. of albumin and more than 10 white blood cells per high-power field on two or more postoperative days. To be called a "morbidity" the patients, in addition, had to run a temperature of 100.4° F. for two consecutive days postoperatively.

Whether cystitis per se causes a rise in temperature or not remains a matter of urologic controversy. It is claimed that, because of the inability of the bladder mucosa to absorb toxins, the temperature elevations in infections of this kind are due to involvement of other parts of the urinary tract or to an entirely different cause. After studying a number of these types of infection in a previous study, the authors noted that in patients with evidence of postoperative urinary tract infection the majority of them developed a rather characteristic temperature rise on the fourth or fifth postoperative day. We feel that without further investigation involving considerable instrumentation, one cannot definitely say these infections are limited to the bladder. It is well within the realm of probability that the toxins are absorbed from the more receptive walls of the ureters or pelves of the kidneys. We have preferred to use the term "urinary tract infection" rather than cystitis for this reason.

TABLE I. MORBIDITY

	GROSS MORBIDITY			URINARY TRACT INFECTIONS	
	NUMBER	NUMBER MORBID	PER CENT MORBID	NUMBER MORBID	PER CENT OF GROSS MORBIDITY
<i>A. Receiving Prostigmine</i>					
Abdominal	58	23	39.8	7	30.43
Vaginal	27	10	37.0	9	90.0
Total	85	33	38.8	16	48.4
<i>B. Untreated</i>					
Abdominal	58	18	31.0	2	11.1
Vaginal	27	7	25.9	3	42.8
Total	85	25	29.40	5	20.0

Table I shows the morbidity rate of the patients who received prostigmine as compared to those who did not. It also shows the morbidity rate for the abdominal and vaginal operations. The table likewise shows the relation of urinary tract infections to the gross morbidity. The patients who received prostigmine had a gross morbidity rate of 38.8 per cent, while those who did not receive the drug had a gross morbidity rate of 29.4 per cent. For the group receiving prostigmine the percentage of morbidities that were due to urinary tract infections was 30.4 per cent for the abdominal operations and 90 per cent for the vaginal operations. For the untreated group the urinary tract infections comprised only 11.1 per cent of the abdominal operation morbidities and 42.8 per cent of the vaginal operation morbidities.

The effect of prostigmine on the postoperative urinary findings is shown in Table II. The laboratory findings are classified as negative or positive, with the latter being graded quantitatively on the basis of I to IV. It is seen that there is very little difference between the two groups. There were 66 patients in the treated group who had positive laboratory findings, and 64 such patients in the untreated group. This was considered an objective estimation of the effect of the drug as it presented the opportunity of estimating the amount of pus and albumin found postoperatively in the urine.

TABLE II. POSTOPERATIVE URINARY FINDINGS

RECEIVING PROSTIGMINE							UNTREATED				
NEG. LAB FINDINGS		POSITIVE LAB. FINDINGS				NEG. LAB. FINDINGS	POSITIVE LAB. FINDINGS				
		GRADE	I	II	III	IV	GRADE	I	II	III	IV
Abdominal	14		20	19	4	1		17	17	5	1
Vaginal	5		5	10	6	1		5	16	3	0
Total	19		25	29	10	2		22	33	8	1

Not all of the patients with positive urinary findings developed the clinical symptoms of urinary tract infection. The individual symptoms of dysuria, frequency, urgency, and burning were taken collectively and classified simply under a general heading of symptoms. Of the 170 patients, there were 84 who had urinary symptoms following surgery. There were 40 such patients in the group receiving prostigmine and 44 patients in the untreated group, indicating no marked difference between the two groups. There was no perceptible difference as to the severity of the symptoms in the two groups.

There were a number of patients in the series who developed all the clinical symptoms of urinary tract infection as well as positive laboratory findings, but who did not show the temperature rise which is usually seen on the fourth or fifth postoperative day. There were nine such instances in the patients who received prostigmine, and eight in the untreated group.

The patients who did not receive prostigmine were on the following catheterization schedule: If they did not void spontaneously within ten hours postoperative, they were catheterized. Once catheterized, catheterization was repeated every eight hours until the "residual urine" was under 150 c.c. and then twice a day until it was under 30 c.c. If, on the first catheterization, less than 30 c.c. was obtained, the catheterization was not repeated. All patients were catheterized at once for distress or distention. If, after voiding, a patient was found to have over 30 c.c. of urine remaining in the bladder, this was considered significant and was called "residual urine." This is in contrast to "retention urine" which is the amount of urine obtained from a patient who is unable to void.

The group of patients receiving prostigmine was divided into two subgroups, A and B. The patients in subgroup A were subjected to catheterization following each voiding; every eight hours if the patient did not void, and as necessary for distress or distention. The subgroup B patients were catheterized only once a day for "residual urine," usually at the hour of sleep, and were not catheterized during the rest of the twenty-four-hour period unless they were distressed or distended.

These groups were established for the purpose of determining the amount of urine (1) residual in the bladder after each voiding, and (2) the amount accumulated or retained in a twenty-four-hour period.

TABLE III. AVERAGE VOLUME AND NUMBER OF CATHETERIZATIONS

	ABDOMINAL	VAGINAL
<i>Untreated</i>		
Average No. of cath. in 10-day period	10.5	16.7
Average c.c. per cath.	187	261
<i>Receiving Prostigmine</i>		
Average No. of c.c. per cath.		
Subgroup A	153	261
Subgroup B	128	127
Patients who voided spontaneously but were cath.		
c.c. per cath.	167	130

The average amount of urine obtained per catheterization was computed. The figures were obtained by averaging individual catheterizations in each group for the first ten postoperative days. Table III shows the results of these computations. The average number of catheterizations in the untreated group was 16.5 times for the ten-day postoperative period.

in the abdominal operations, and 16.7 times for the same period in the vaginal procedures. The average amount of urine obtained in the abdominal operations was 187 c.c. per catheterization, and in the vaginal operations 261 c.c. in the untreated groups.

The average number of catheterizations for the group receiving prostigmine was not computed because every patient receiving prostigmine was subjected to catheterization according to the subgroup in which the patients were alternately placed.

In the groups receiving prostigmine it was found that in subgroup A, or the patients catheterized after each voiding, the average amount of "residual urine" obtained on catheterization was 153 c.c. per catheterization for the abdominal procedures, and 261 c.c. per catheterization for the vaginal procedures. In subgroup B, or the group catheterized once daily at the hour of sleep, the average amount of urine obtained on each catheterization was 128 c.c. for the abdominal operations, and 127 c.c. for the vaginal operations. It is observed that the average amount of urine obtained in the vaginal group was much less in those who were catheterized only once a day than in subgroup A.

It has been thought that if a patient voided spontaneously within the first ten hours postoperatively, there was no need to catheterize her unless symptoms of urinary distress appeared. In 38 patients who voided spontaneously within twelve hours postoperatively, and were also catheterized, the average amount of "residual urine" was 167 c.c. per catheterization in abdominal operations and 130 c.c. per catheterization in vaginal procedures.

There were 21 patients who did not receive prostigmine but voided spontaneously and did not have any catheterizations. They had a gross morbidity rate of 43 per cent as compared to a morbidity rate of 29.4 per cent for the untreated group as a whole. It is difficult to evaluate this group for, in the absence of catheterizations and lack of symptoms of urinary tract distress, the urinary tract cannot be blamed or exonerated as the etiological factor of morbidity. In view of the fact that patients who voided spontaneously and were catheterized showed a definite "residual urine," one can assume these patients also ran a "residual urine" with its potential dangers. It cannot be said, however, that the urinary tract was responsible for the morbid condition in these cases.

Abdominal "Gas Pains"

To study the effect of prostigmine on "gas pains" an arbitrary classification was set up. Based principally on the patient's complaints as to the severity of the pains, the discomfort was classified on the basis of I to IV. Table IV shows the number of patients in each of the groups in relation to the severity of pain, distribution, and general abdominal discomfort. It would appear that in the group receiving prostigmine there was some diminution in the severity of pains; in Group II the number is considerably diminished. In Groups III and IV, or most severe pains, the number is twice as high in the group receiving prostigmine.

TABLE IV. POSTOPERATIVE ABDOMINAL "GAS PAINS"

	RECEIVING PROSTIGMINE					UNTREATED				
	NONE	GRADE				NONE	GRADE			
		I	II	III	IV		I	II	III	IV
Abdominal	18	9	17	11	2	9	5	49	5	0
Vaginal	12	3	11	1	0	16	2	8	1	0
Total	30	12	28	12	2	25	7	57	6	0

Discussion

The importance of the postoperative care of the urinary bladder following gynecologic surgery is well recognized by all surgeons doing this type of work. "Residual urine" has long been emphasized as the principal cause of urinary

tract infections. Nearly twenty-five years ago Curtis⁶⁻⁸ showed that the number of urinary tract infections resulting from "residual urine" was far greater than the infection arising from repeated catheterizations. He brought out the important fact that the catheter itself is not the principal source of infection, but that the danger lies in the retention of urine in the bladder, comparable to the "sink which drains inadequately."

Because of the bladder's precarious position lying anterior to the uterus, it is subjected to traumatization in both abdominal and vaginal surgery. In addition to injury to the bladder from instruments and dissection, the innervation of the bladder is disturbed in gynecologic operations. Although the innervation of the bladder remains a urologic controversy, it is generally assumed that the parasympathetic nerves from the hypogastric vesical plexus are responsible for the contractibility and tone of the bladder. Since these nerves enter the bladder under the lateral reflection of the pelvic peritoneum, it is understandable why the bladder physiology is disturbed following pelvic surgery.

Prostigmine methylsulfate is a parasympathetic stimulator. It has been thought, therefore, that this drug would restore the tones of the bladder and initiate voiding following surgical procedures in the pelvis. Experimentally, Bross and Kubikowski⁹ have shown that prostigmine causes contraction of the excised bladder in the rabbit and guinea pig. It has been felt that if bladder tone could be maintained following surgery, postoperative urinary retention could be avoided.

In our series of patients the effect of prostigmine was studied from several aspects. It is seen (Table I) that the morbidity rate was not decreased by the use of the drug in either the abdominal or the vaginal procedure. The morbidity rates in each of the groups is comparable to the over-all morbidity rates for hysterectomy found by the authors in a previous study.¹ The causes of morbidity show that the group receiving prostigmine had three times the incidence of cystitis as did the untreated group. These were cases of proved urinary tract infection with the temperature rises characteristic of this condition. There were approximately the same number of patients in each group who developed cystitis without a temperature rise.

The vaginal procedures as a group showed a lower incidence of urinary tract infection than was expected, but the group receiving prostigmine developed a high number of bladder infections.

In examining the laboratory findings of the urine postoperatively, where the findings are graded negative or positive on the basis of I to IV according to the quantitative findings, there is practically no difference between the treated and untreated groups. From this part of the study, it is evident that prostigmine did not materially affect the postoperative urinary laboratory findings.

A more subjective approach to the problem is through the study of postoperative urinary symptoms. Both Curtis⁸ and Danforth¹⁰ emphasize the importance of urinary distress, urgency, frequency, and dysuria, in determining the ability of the patient to empty her own bladder. It is seen from the study that there was little difference between the treated and untreated groups as to

the development of urinary distress following surgery. While more of the patients undergoing vaginal procedures were free of urinary discomfort in the untreated group, the abdominal operations had a somewhat higher incidence of symptoms in the group receiving prostigmine.

It has been taught that a patient voiding spontaneously within ten hours postoperatively, and free of urinary distress, does not need to be catheterized. It was believed that this type of patient emptied her bladder, and, if not catheterized, remained free of urinary tract infection. Curtis⁸ states: "If the patient suffers no discomfort from inability to urinate after her return from the operating room there is no need for catheterization; moreover, the bladder tends to remain free from infection until a catheter has been used." Danforth says: "After operation, if the bladder is emptied spontaneously, and if no vesical discomfort is felt, it may be left undisturbed."

In the group receiving prostigmine, catheterizations were carried out in all patients whether they voided spontaneously or not. It was found that the patients who voided spontaneously carried a rather large amount of "residual urine." It was shown that in these patients the amount of urine obtained by catheterization after spontaneous voiding within ten hours postoperatively was similar to that obtained from patients catheterized because of urinary retention or distress. Therefore, the mere fact that the patient voids spontaneously does not eliminate the potential danger of "residual urine." It is often assumed that if the patient is voiding freely without symptoms of urinary distress, the bladder is emptying itself and cannot be held responsible for an insidious temperature. The authors feel that this problem of "residual urine" in patients with spontaneous voiding following surgery is of fundamental importance. It can be eliminated only by constant awareness of its existence. They feel, as Curtis has repeatedly stated, that the principal danger in postoperative urinary tract infection lies in the "contaminated sink" of the unemptied bladder.

The importance of careful catheterization technique in this regard cannot be too strongly emphasized. Unquestionably, faulty catheterization technique without proper aseptic precautions is responsible for a high percentage of urinary infections. With proper asepsis the risk is minimal. It cannot be said that the use of the catheter does not cause cystitis and urinary tract infection. Catheterization can, and does, introduce bacteria into the bladder and urinary tract. It is a question which is the greater evil, the catheterization or the "residual urine," retention, and distention.

We felt that the patients receiving prostigmine were benefited as far as "gas pains" were concerned. This was the conclusion from the semiobjective classification of the severity of the patient's discomfort and the subjective observation of those who were charged with the care of the patient. It was also observed, and brought out in Table IV, that when a patient apparently had an intestinal obstruction, functional or mechanical, the use of prostigmine tended to increase the severity of the pain, and relief was not obtained until the obstruction was relieved. This is to be expected from the physiologic action of the drug and accounts for those patients whose pains fell in Grades III and IV in the treated group.

Conclusions

1. A study of the effect of prostigmine on the urinary tract following gynecologic surgery is presented, with 85 patients receiving the drug and 85 patients used as controls.
2. The incidence of postoperative urinary distress was the same in the treated as in the untreated group.
3. The postoperative urinary laboratory findings were the same for both groups.
4. The incidence of postoperative spontaneous voiding was the same in both groups.
5. "Gas pains" were somewhat lessened in the patients receiving prostigmine, but where obstruction existed, the discomfort was increased by prostigmine.
6. The amount of "residual urine" was found to be the same in the patients who voided spontaneously as in those who had to be catheterized for urinary distress or distention.
7. Prostigmine was ineffective in preventing postoperative urinary infections as it was used in this study.

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104 S. MICHIGAN AVENUE

Discussion

DR. VINCENT J. O'CONOR.—In the expulsion of ureteral calculi, prostigmine seems to have been of great help where the lower end of the ureter is not constricted, and where the ureter has been previously dilated, and the orifice enlarged. We have been surprised by having very sizable stones pass after injection of prostigmine. At other times, we have had very discouraging results when we thought prostigmine should have given us more aid than it did.

These clinical papers point out that, in spite of the parasympathetic effect which prostigmine has on the bowel and perhaps the ureter, a comparable effect on the bladder is not obtained. Nesbit and Cummings of Ann Arbor gave a paper at a meeting of the Genito-Urinary Surgeons in which they compared 235 patients with appendectomy, in which 17.5 per cent required postoperative catheterization, with 65 cases in which prostigmine was used as a prophylactic and therapeutic agent. The doses given in their series were much the same as Drs. Jones and Doyle have used, namely, 1 c.c. thirty-six hours before operation, 1 c.c. every four hours postoperative, and then 1 c.c. every six hours. If the patient developed discomfort and did not void, he was given a dose every hour. Quite a large percentage still required catheterization. In Gordon's series, 18.5 per cent required catheterization. Both of these series paralleled the findings of Drs. Jones and Doyle.

I would like to ask the gynecologists a few questions from a urologic point of view in regard to catheterization. How long should a patient be allowed to go before catheterization is performed? What procedures are used to encourage spontaneous urination other than prostigmine? Has postural help been given? Has stimulation of the rectal sphincter been given by means of a low return-flow enema or warm glycerin per rectum? How often do you use hot vaginal douches, a procedure that we all know will stimulate urination? It seems to me that a study which has to do with the incidence of catheterization must take into consideration the history and clinical problems of the patient. It is a question of judgment as to when to catheterize.

Catheter technique seems to me to be the real problem that faces us in regard to the figures of postoperative morbidity associated with catheterization. Everyone admits that catheterization properly done should be a nontraumatic and a noninfection-producing procedure except perhaps in cases with definite paraurethral gland infection or a circumscribed urethritis.

In many places they put 2 per cent aqueous mercurochrome into the bladder. Even when placed in a normal bladder some patients will get a violent reaction, with hyperemia, which will add to the bladder neck obstruction. I have been in hospitals where I see them routinely using $\frac{1}{4}$ to $\frac{1}{2}$ per cent silver nitrate solution. This is not rational. If you introduce silver nitrate into the bladder, urethra, or kidney pelvis over a period of time, you will have a precipitate of silver in the mucosa, with a resulting round-cell infiltration. If you are trying to stimulate the mucous membrane to free itself of a chronic interstitial infection, then there is some rationale for putting silver salts against the mucosa, but is it a good prophylactic procedure when you are introducing it for catheterization?

Just as a matter of interest I picked up some catheters that are used in the hospital. If you look at the instrument case you will see that 50 per cent of the catheters have been boiled and boiled to a point where they do a figure-of-eight when inserted into the bladder. There are catheters made especially for women and, if they are properly sterilized and properly handled, and the nurses are instructed in their use, there will be less chance of causing trauma to the urethra.

If a patient persists in showing residual urine after several catheterizations, intermittent catheterization should be done. If you are going to perform intermittent catheterization, is eight hours often enough? Are you correlating the patient's intake with the amount of urine obtained at catheterization? One patient may not total 200 c.c. in eight hours, while another patient may have 1,000 c.c. in the bladder at that time.

How do we know that 150 c.c. of residual urine is more harmful to the patient than 30 or 60 c.c. of residual urine, provided the patient is not having distressing symptoms? Whatever injury or dysfunction occurs in most of this pelvic surgery, we all agree, is a transitory thing. Our objective should be to devise a method of management so that when the patient's bladder tone and vis a tergo returns to normal, as it does in practically all instances, the patient will not have acquired some permanent dysfunction or inflammation as a result. We should supervise the management and follow it through in such a rational way that late urinary pathology does not result.

CYCLIC VARIATIONS IN THE VISCOSITY OF CERVICAL MUCUS AND ITS CORRELATION WITH AMOUNT OF SECRETION AND BASAL TEMPERATURE*

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THE event of ovulation is doubtless of greater biologic significance than the more apparent phenomenon of menstruation, for upon its occurrence depend the periodic intervals of fertility. The egg, after leaving the ovary, cannot for long await the arrival of the sperm. Hence, for a planned pregnancy, the meeting of the egg and the sperm must coincide with the time when the former is susceptible to fertilization.

In the investigation of sterility of the female it is important to know if and when ovulation is occurring. Menstruation without ovulation is not uncommon. Furthermore, the fertile period in one cycle may not correspond to that in another cycle, even in the same individual. Although actual observation of ovulation is not clinically practicable, it is nevertheless possible with indirect methods to determine its occurrence by a study of related phenomena. Thus, familiar tests such as endometrial biopsies, vaginal smears, and hormone assays may well tell of the period of ovulation. Observation of the shift of the basal body temperature offers a less troublesome and time-consuming method for recognizing this period of the menstrual cycle in many women.

Séguy and Vimeux,¹ in 1933, reported cyclic changes in the amount of cervical mucus in normally menstruating women. A great increase in quantity was observed between the tenth and fifteenth days of the menstrual cycle. At this time the mucus is glairy, transparent, and relatively acellular. In a later paper Séguy and Simonnet² correlated this phenomenon of increased mucus production with an increase in urinary folliculin and evidence of ovulation as verified by inspection of the ovaries at laparotomy. These observations were confirmed by Lamar, Shettles, and Delfs,³ who extended them by noting with in vitro studies, that spermatozoa can penetrate the mucus to an appreciable distance only during this period of increased secretion associated with low viscosity, and during menstruation.

The present authors⁴ made daily observations on a series of normal subjects and determined the quantity of cervical mucus present by objective methods. These data were correlated with the basal body temperature curves, and it was noted that the period of the cycle when the amount of mucus is greatest corresponds to the time of the temperature shift from a lower to a higher level, i.e., the presumptive time of ovulation.

On the basis of previous work,² it would appear that the viscosity of the cervical mucus is an important factor in determining its penetrability by

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spermatozoa. No satisfactory method has been available for measuring this physical characteristic, and, as a result, workers in the past have estimated the viscosity as high, moderate, or low, depending upon the ease with which the mucus could be drawn into a small capillary tube. Cervical mucus is not a homogeneous substance. Fractions of a single sample may vary in consistency as does the white of an egg. Opalescent areas, having a thicker consistency than the adjacent more fluid portion, may be clearly visible to the naked eye. The tackiness, also a variable factor, may likewise influence the rate of flow of the mucus. But more important, the quantity of material available for study may frequently be as little as 25 to 50 milligrams. These facts doubtless have been the reasons why a suitable objective method for the measurement of the viscosity of cervical mucus has not been employed heretofore.

The method described below has circumvented at least some of these difficulties and has proved useful in determining the cyclic variations in the viscosity of cervical mucus in normal women.

Subjects

During the course of this study four young healthy women were used as subjects. With but few exceptions, aside from the time of menstruation, daily observations were made. One subject was followed through two cycles, and the other three, through four cycles each.

Methods

Basal Body Temperature.—Each subject took her basal vaginal temperature in the morning before arising. The Fahrenheit scale was read to the nearest 0.1 degree. The shift in temperature from a relatively lower level during the follicular stage to a relatively higher level, where it is maintained throughout the progestational phase, is held to mark the approximate time of ovulation.^{5, 6} Due allowance must, however, be accorded any intervening infection, which of itself might affect the temperature and thereby obscure the ovulatory temperature shift. The menstrual periods and the temperature shift were taken as more or less fixed points of reference in each cycle.

Collection of Material.—An unlubricated speculum is inserted into the vagina to expose the cervix. Mucus from the cervix is drawn by aspiration into a weighed glass cannula, the amount being determined by difference. An attempt is made in each case to evacuate the cervical canal completely, a second cannula being used when necessary. The mucus covering the external os is considered along with that from within the canal in the determination of the total quantity present. Because mucus at the external os may well be altered by the vaginal environment, only that mucus which is obtained from within the canal has been used in the viscosity studies.

Viscosity.—The apparatus for measuring viscosity is shown in Fig. 1. A glass capillary tube approximately 0.4 mm. in internal diameter and about 15 cm. in length is mounted in a horizontal position on a wooden block (*a*) alongside of which is fixed a millimeter scale. The capillary tube is fused to a tube of slightly wider bore in which a stopcock is inserted. This in turn is connected through an airtight 500 c.c. flask (*c*) to a mercury manometer (*d*). The flask serves to keep the pressure constant in the system.

Since the viscosity of cervical mucus is so much greater in the preovulatory and postovulatory phases than in the ovulatory period, no one reference fluid is applicable throughout the cycle. As used here, the term viscosity is defined as the time in seconds required to draw a column of mucus through the capillary tube a given distance at a given pressure as measured on the mercury manometer.

The mucus, after being expelled from the cannula, is placed in the wide end of the small funnel, which is then placed horizontally in position so that the tip of the capillary dips into the mucus. Sufficient pressure is applied to draw the mucus into the capillary. Due to the viscid nature of the mucus it is difficult to fill the capillary to exactly the same length each time, but a column of approximately 4 cm. is usually used. Because the mucus does not break cleanly, it is necessary to cut the thread of mucus between the capillary and the funnel when the latter is removed. The tip of the capillary is then wiped clean. The time in seconds for the head of the column to travel 3.0 cm. under a given pressure is measured with a stop watch.

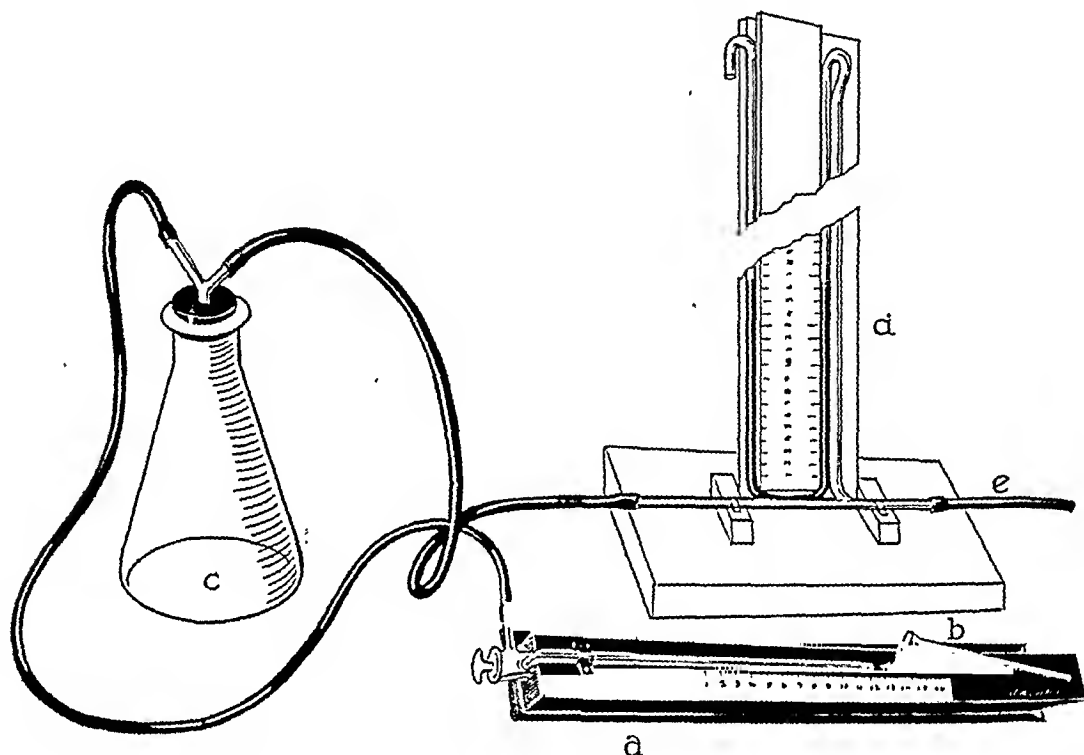


Fig. 1.—Apparatus for measuring the viscosity of cervical mucus. *a*, Capillary tube mounted horizontally on wooden block with millimeter scale in position; *b*, funnel used as reservoir for filling capillary; *c*, 500 c.c. air-tight flask; *d*, mercury manometer; *e*, outlet for applying suction.

A pressure of 4.1 cm. of mercury is used whenever possible. If this is insufficient due to a marked increase in the viscosity of the mucus, pressures of 6 or 8 cm. are used. It is difficult to draw up the column of mucus intact because of its adhesiveness. To correct for the loss on the walls of the capillary tube, the length of the column is noted at the beginning and again at the end of the determination, and the average of these two figures is used in the calculation.

In order to compare the daily determinations, all observations are corrected to conform with arbitrarily chosen standards. A pressure of 4.1 cm. of mercury is used as the standard as the majority of samples can be measured directly at this pressure. It has been determined that, in about 80 per cent of the cases, the time required to draw up the column of mucus is approximately inversely proportional to the pressure. Therefore, when a higher pressure is used, the appropriate correction is applied. An average length of 4.0 cm. has been chosen as the standard column length. Experiments show that the time required to move the column of mucus is directly proportional to the length of the column. Therefore, when the average column length is not 4.0 cm., the appropriate corrections are made. The distance of 3.0 cm. for the column of mucus to travel seems best adapted to the equipment.

Duplicate observations were made whenever possible. Inasmuch as it requires 25 to 30 mg. of material for a single determination, duplicate determinations usually cannot be done except during the period of increased secretion.

Experiment has shown that the viscosity is altered when the mucus is permitted to stand for more than several hours. For this reason determinations should be performed promptly.

Penetrability.—The method of Lamar, Shettles, and Delfs³ has been used for observing in vitro the penetrability of cervical mucus. A small amount of mucus is drawn up into a capillary tube of 0.3 to 0.4 mm. internal diameter. A column of fresh semen is then drawn in, leaving a small bubble of air between the mucus and the semen to prevent mechanical mixing and also to serve as a reference point in observing the penetration. The time at which the capillary is prepared is noted. The capillary tube is then placed on a slide, covered with mineral oil to reduce refraction, and the penetration of the sperm into the mucus is observed through the microscope. By using a stop watch and a calibrated mechanical stage, the rate of penetrability can be measured.

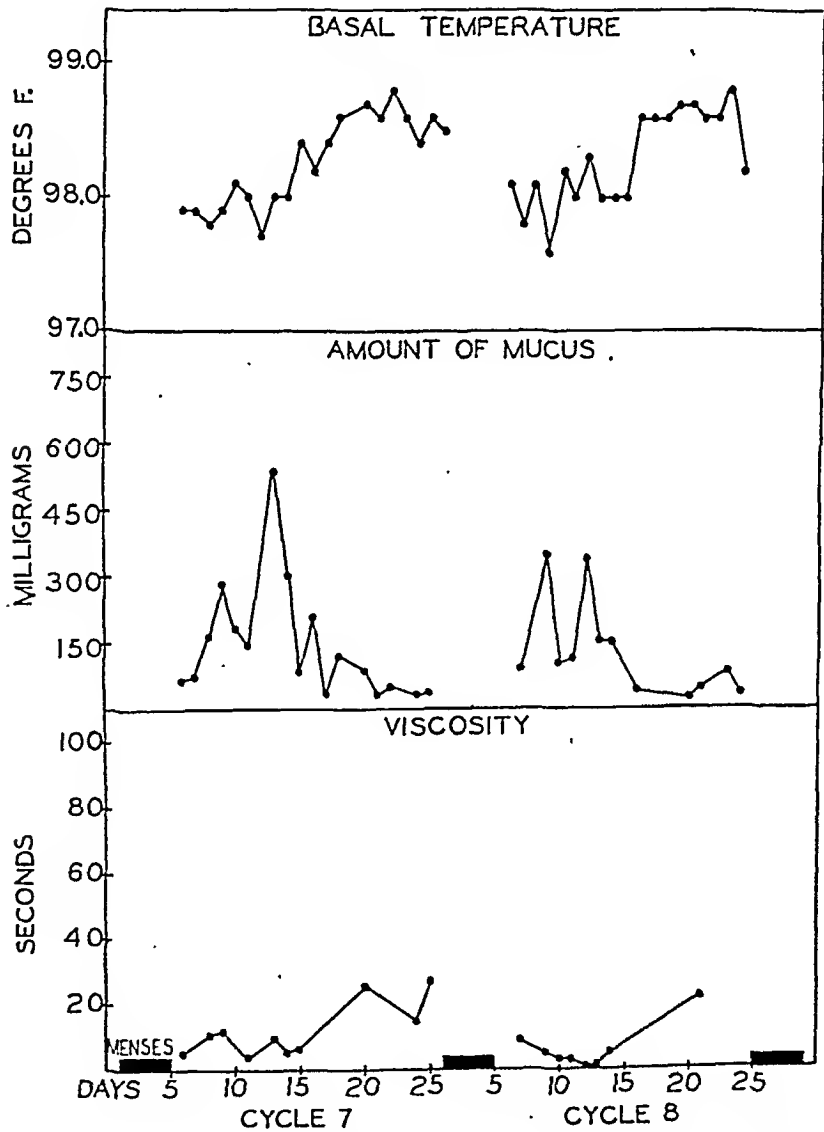


Fig. 2.—Relation between basal temperature, amount and viscosity of cervical mucus for Subject 5, a 32-year-old gravida I. Cycles 7 and 8 were consecutive.

Results

A total of 14 cycles on four subjects have been studied. The results are shown in Figs. 2, 3, 4, and 5. Because the time of the ovulatory period may vary from one cycle to another even in the same individual, each cycle is shown separately so that the marked changes are more sharply delineated.

Inspection of the curves shows that there are characteristic cyclic fluctuations in basal temperature, amount and viscosity of mucus. Fairly constant points are noted to occur at about the middle of each cycle in practically every instance. Occurrence of these shifts at approximately the same time suggest that they are associated phenomena. Since they occur at the supposed time of ovulation, it seems probable that they are related to this event.

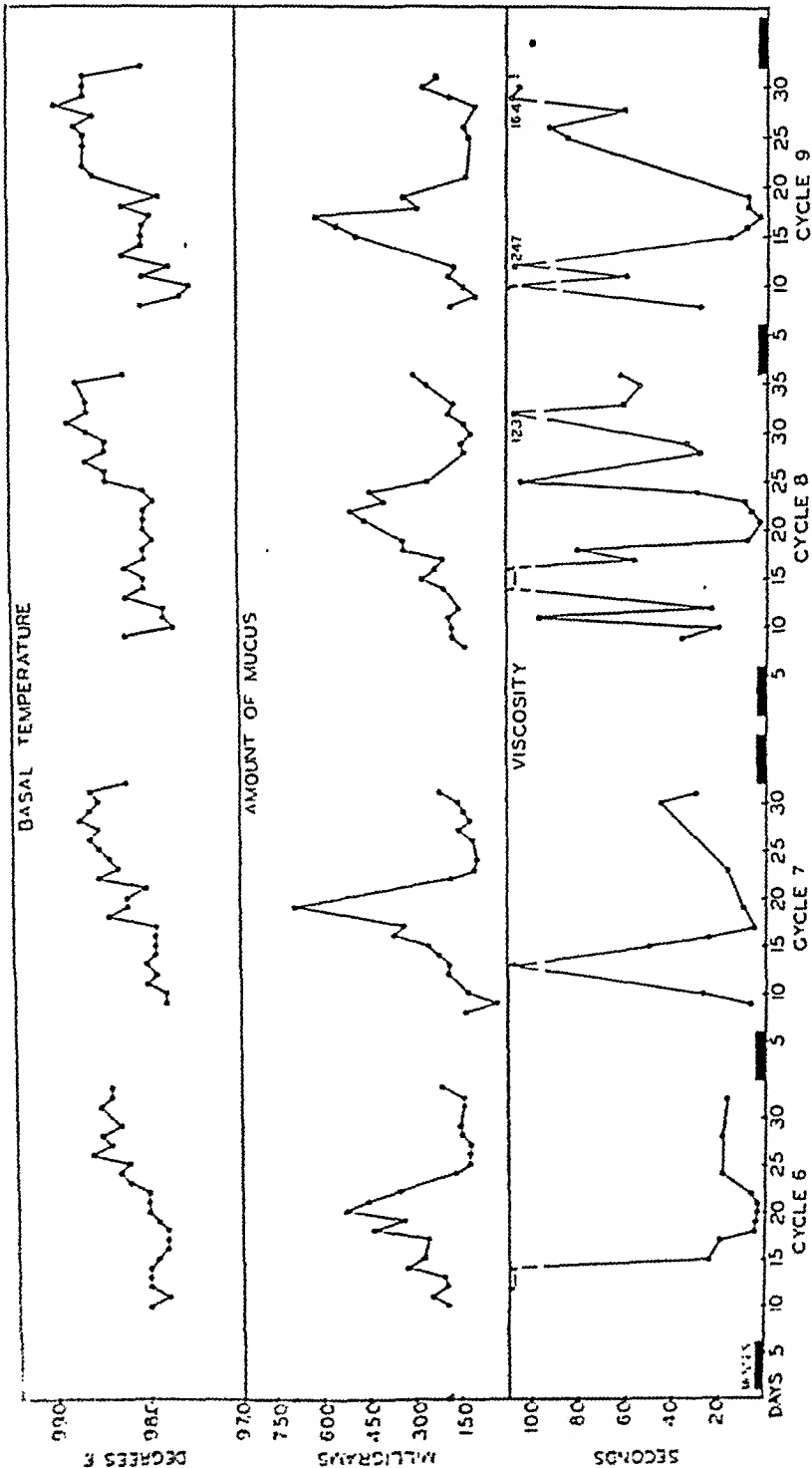


Fig. 3.—Relation between basal temperature, amount and viscosity of cervical mucus for Subject 6, a 25-year-old nullipara. Cycles 6 and 7 were consecutive, as were Cycles 8 and 9. In the viscosity curve, 7 indicates that the viscosity was beyond the range of the method, and 6 indicates that a pressure greater than 4.1 cm. was necessary to move the column, the appropriate corrections having been applied.

The relation between the decrease in viscosity and the increase in amount of mucus is especially close, the two phenomena occurring almost simultaneously. Studies now in progress indicate that the water content of the mucus also increases at this time. The viscosity was

measured on specimens of mucus obtained on 163 different days. On 47 other days insufficient mucus was obtainable from the canal to do determinations. Inasmuch as the amount is increased during the ovulatory period, it follows that these 47 days were from the other phases of the cycle. In 39 of the 163 instances a pressure of 4.1 cm. of mercury was inadequate

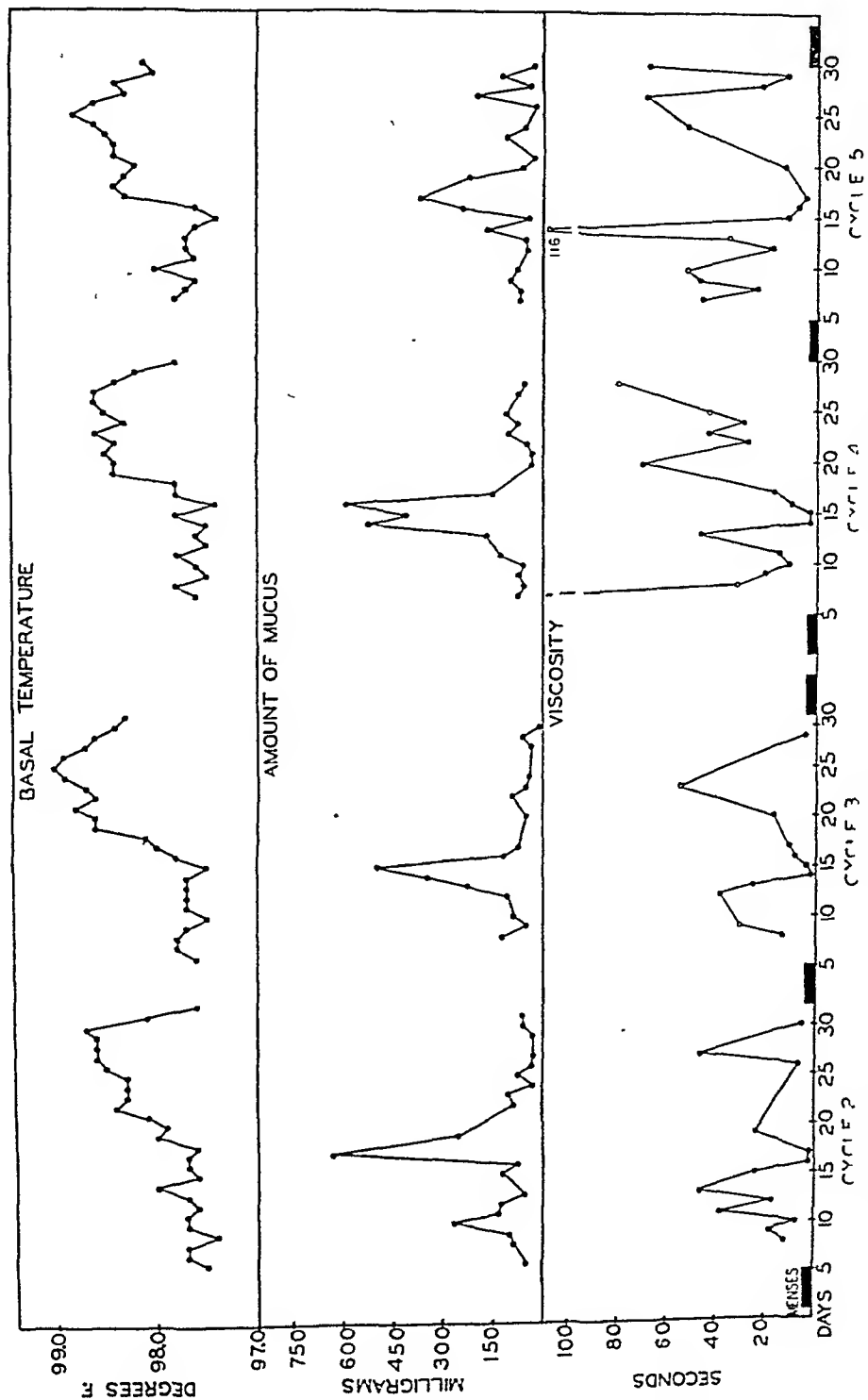


Fig. 1.—Relation between basal temperature, amount and viscosity of cervical mucus for Subject 7, a 21-year-old nullipara. Cycles 2 and 3 were consecutive, as were Cycles 1 and 5. Symbols as explained under Fig. 3.

to pull the column of mucus up the capillary tube. Only 1 of the 39 occurred during the ovulatory period, the remainder being about equally divided between the preovulatory and the postovulatory phases. Enough material to do duplicate determinations was obtainable on 59 days. Of these, 62.7 per cent checked within 3 seconds and 72.9 per cent checked within

5 seconds. Considering the heterogeneous character of cervical mucus, checks of 5 seconds or less were considered satisfactory.

Small day by day fluctuations in basal temperature, amount and viscosity of the mucus may be noted in the preovulatory and postovulatory phases of the cycle. Although they

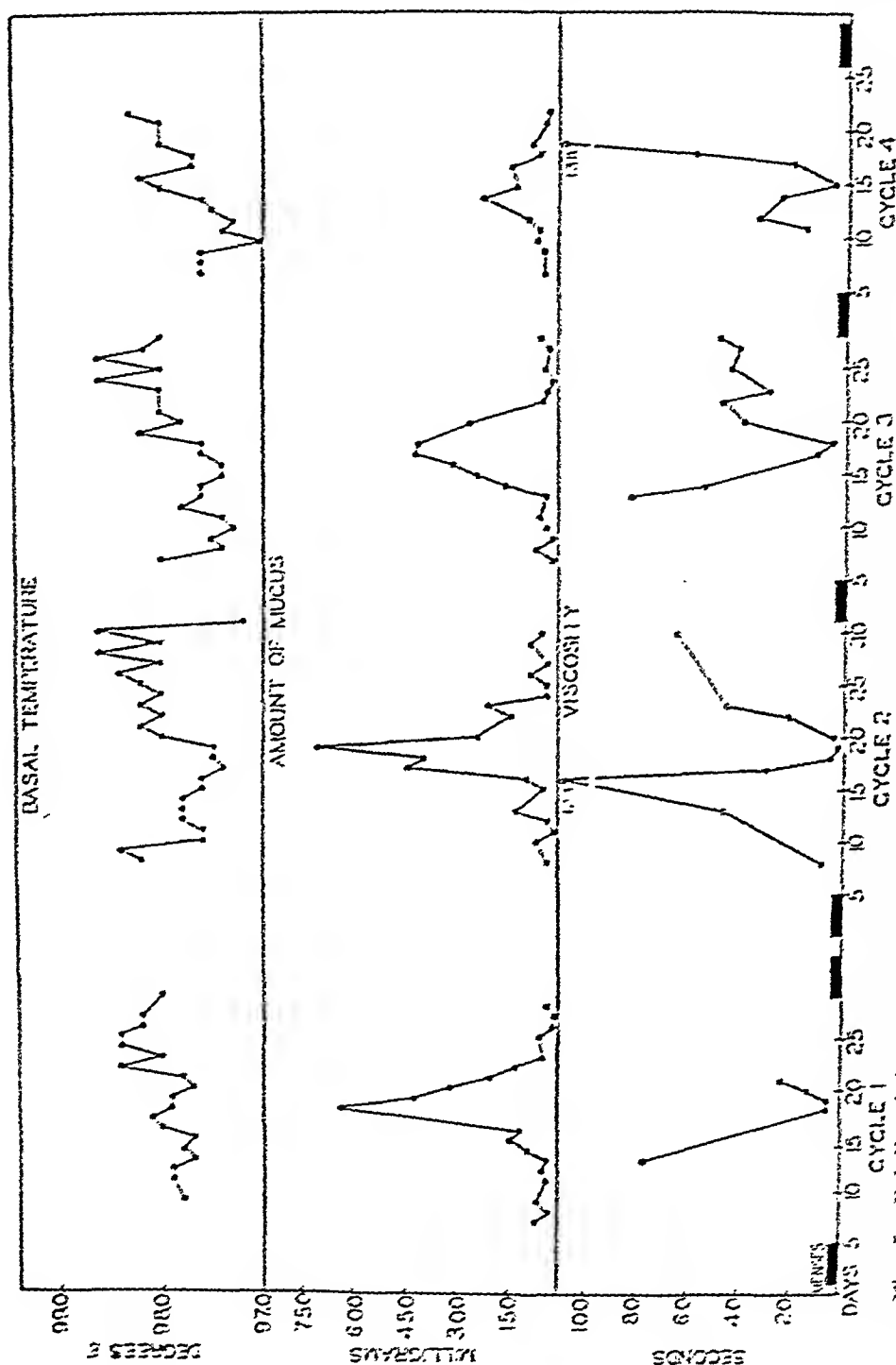


Fig. 5.—Relation between basal temperature, amount and viscosity of cervical mucus for Subject S, a 24-year-old multipara. Cycles 2, 3, and 4 were consecutive. Cycle 4 was not completed because of illness after the twenty-first day. Synchoda was expelled under fig. 3.

do not compare in magnitude with the changes found during the ovulatory period, they are nevertheless apparent. The fact that standard conditions could not be set up controlling the temperature of the room, the amount of sleep, the diet, or the occurrence of mild infection, might explain these minor variations in the basal temperature. This does not greatly affect.

the observed temperature shift in mid-cycle. The quantity of mucus in the cervical canal and about the external os may depend on the accumulation there, and this in turn may depend on posture, the upright position presumably favoring drainage, although this is conjectural. Whatever the cause of these minor fluctuations, the data certainly show marked differences in the amount obtainable in the various phases of the cycle, the peak production occurring at the time associated with ovulation. Daily fluctuations are also noted in the viscosity of the mucus. As has been stated previously, this material is by no means homogeneous. In addition to variation in the cellular content there is probably also considerable difference in the tackiness of the mucus. These changes in tackiness undoubtedly modify the readings as obtained with the apparatus used. Nevertheless, during the ovulatory period, the figures all show characteristic and distinct periods of low viscosity corresponding to the approximate time of the temperature shift and to the period when the amount of secretion reaches its height. Only relatively low pressure is required to measure the viscosity at this time.

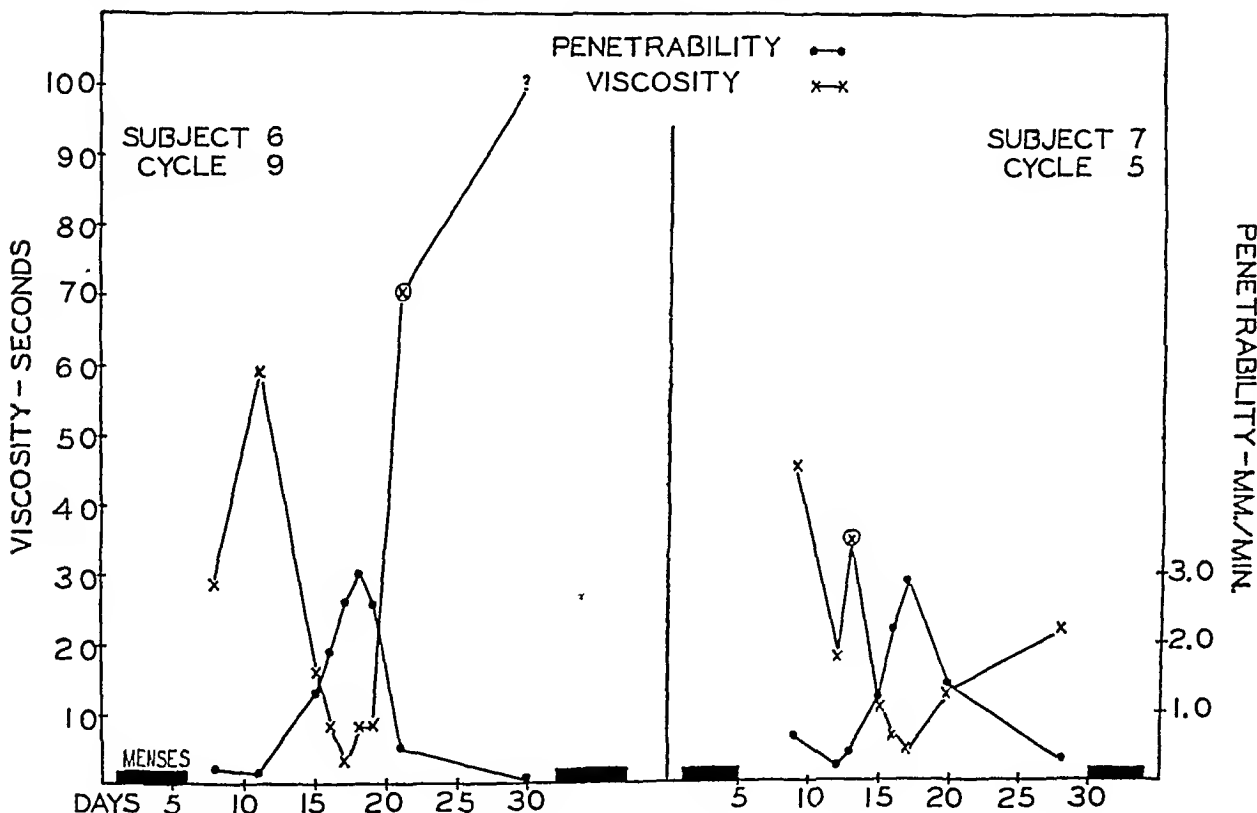


Fig. 6.—Relation between the viscosity and the penetrability of cervical mucus by spermatozoa.

The correlation between the viscosity and the penetrability of cervical mucus by spermatozoa was studied in two cycles and the results are shown in Fig. 6. It is apparent that the two are closely related, the maximum penetrability being associated with the minimum viscosity. Although this finding was to be expected in view of Lamar's work, it was the first comparison between the two when the viscosity was measured by an objective method. It is not known whether or not the viscosity is per se the factor which determines the degree of penetrability, but the above observations seem to suggest such an interrelationship.

Comment

It would appear from these studies that the ovulatory process in normal subjects has remote manifestations in that it is characterized by a period of increase in the secretion and a decrease in the viscosity of the cervical mucus, along with a shift in the basal temperature. Since these events occur during

the same short period of time, which presumably marks the time of ovulation, a study of these fluctuations might give information concerning the likely time of conception and might help explain certain cases of sterility.

The authors have studied two patients with otherwise unexplained sterility who showed atypical curves when compared with normals. In the first case the amount of mucus increased normally and the vaginal temperature curve suggested that ovulation was occurring. The viscosity, however, remained very high throughout the cycle, never being less than 25 seconds. Also the mucus never became transparent and always showed a high cellular content. The reason for this high viscosity is practically impossible to determine with present methods, but until it can be decreased at the proper time in the cycle, it is doubtful whether the spermatozoa could traverse the cervical canal.

In the other cases the cycles were slightly irregular. In two cycles the vaginal temperature curves resembled the anovulatory type in that there were no definite cyclical patterns, and neither was there any cyclic change in the amount of mucus. In a third cycle the amount of mucus increased in mid-cycle and the temperature curve showed a definite rise at this time. However, the temperature had fallen to the preovulatory level four days after the rise and remained at this low level for the rest of the cycle, making it appear that the corpus luteum did not persist as in the normal individual.

Summary

1. An objective method for measuring the viscosity of cervical mucus has been presented.

2. Cyclic variations in basal temperature, and amount and viscosity of cervical mucus have been observed in normal young women.

3. The viscosity is decreased during the period of increased secretion, both phenomena occurring at approximately mid-cycle. At this time a shift in the basal temperature occurs, this shift being useful for fixing the approximate time of ovulation.

4. The penetrability of cervical mucus by spermatozoa is correlated with viscosity. Maximum penetrability occurs when the viscosity is lowest.

5. The use of the methods outlined above may prove helpful in the study of sterility.

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TUBAL STERILIZATION

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DURING the last ten years at the Sloane Hospital for Women, we have performed 233 sterilizations by a variety of operations on the Fallopian tubes. In this communication, our indications, methods, and results will be reviewed and the literature will be partially surveyed in an effort to determine which of the many tubal operations advocated offers us a simple, safe, sure, and rapid method of permanently occluding the lumen of the tubes.

"Pregnancy has occurred after all methods of tubal sterilization. Hysterectomy and bilateral salpingoophorectomy are the only possible safeguards." This statement, made by Dr. John Polak,¹ in 1933, still holds good today.

Historical

The first attempt at tubal sterilization recorded in the literature appears to have been performed at Toledo, Ohio, in 1880, at the time of a cesarean section.^{2, 3} A ligature was placed about the tubes 1 inch from each cornua. Between 1880 and 1910, a variety of techniques were attempted with rather poor results. These included ligation, crushing, resection, or a combination of such procedures. Many failures were encountered by Ries, Fraenkel, and Aftergeld, both in animal experimentation and on humans, between 1898 and 1899.⁴⁻⁶ In 1913, Leonard⁷ reviewed the literature and commented on the high incidence of failure following all methods, including resection, cauterization, and total salpingectomy.

In 1919, Madlener⁸ introduced a well-known tubal sterilization, which achieved considerable popularity on the continent, especially in Germany. In this operation, a small knuckle of tube is crushed, and a ligature of nonabsorbable suture material is placed across the devitalized area (Fig. 1). In 1921, J. Whitridge Williams⁹ discussed sterilization in detail and reviewed 44 cases performed at the Johns Hopkins Hospital. He ventured to predict at this time that the Madlener method would not stand the test of time. In 1926, and again in 1932, Madlener^{9, 10} reported on two additional series of cases with no known failures. By this time, however, scattered reports of failure of this operation to prevent pregnancy began to appear in the literature.¹¹⁻¹⁴ Von Graff,¹⁵ reviewed the subject up to 1938. He collected 4,279 Madlener sterilizations with 19 known failures. His table is brought up to date with the addition of ten other reports (Table I).

At least one hundred other methods of tubal sterilizations have been described, including knotting of the tubes. The majority of these operations are minor variations on one or two basic themes. All have resulted in a variable number of failures.

Cornual resection, once considered foolproof, has not stood the test of time any better than other methods (Fig. 2). In this operation a wedge-shaped mass of tissue from the uterine cornu is excised along with the tubal isthmus. Numerous failures following this operation are encountered in the literature.^{9, 16-20} Nurnberger¹⁶ estimated the incidence of failure of cornual resection to be about 7.7 per cent. This high incidence is not surprising, inasmuch as pregnancy has developed after salpingectomy and supravaginal hysterectomy.²¹

A variety of segmental resections have been reported. Many of these operations include burial of one or both tubal stumps between the leaves of the broad ligaments. This type of operation is highly recommended by Watson, who has never had a failure (Fig. 3). However, there are reports in the literature of pregnancy following this type of sterilization.²²

TABLE I. REPORTED SERIES OF MADLENER STERILIZATIONS

AUTHOR AND YEAR	NUMBER OF CASES	NUMBER OF FAILURES	PER CENT
Von Graff ¹⁵ (Lit to 1938)	4,279	19	0.44
Neubauer ³³ 1938	83	2	2.4
Adair and Brown ³⁴ 1939	50	0	0
Lazard ³⁵ 1940	117	1	0.85
Dippel ³⁰ 1940	101	5	4.9
Hewitt and Whitley ³⁶ 1940	100	0	0
Brennecke ³⁷ 1941	23	0	0
Pfeutze ³⁸ 1941	165	3	1.9
Thornton ²⁶ 1941	3	0	0
Mays and Dilworth ³⁹ 1941	29	0	0
Lock ²⁷ 1942	2	0	0
TOTALS	4,952	30	0.6

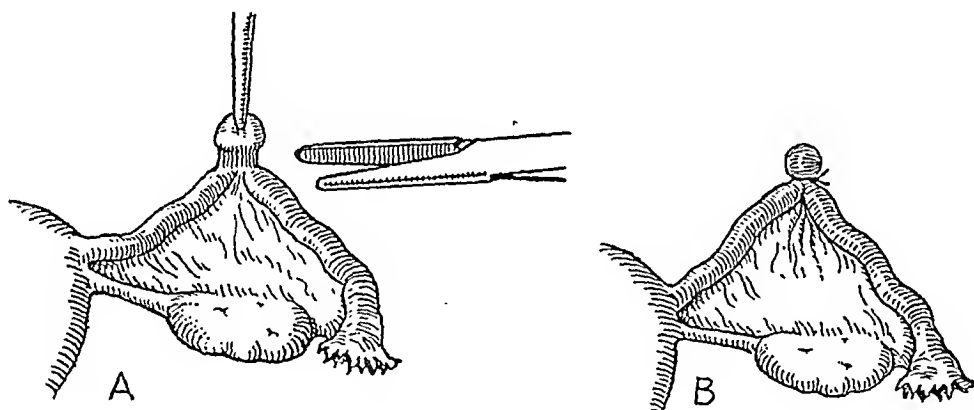


Fig. 1.—The Madlener sterilization.

In 1930, Bishop and Nelms²³ described a simple method of tubal sterilization which had been serving Dr. Ralph Pomeroy well for many years (Fig. 4). Pomeroy claimed no credit for originating this technique. The tube is grasped at its mobile middle third, thus forming a loop. This, with a small portion of mesosalpinx, is ligated without preliminary crushing with fine absorbable catgut. The segment of tube above the ligature is then excised. Bishop's original series consisted of 100 successful cases. From a perusal of the literature, it seems that this operation has not met with full recognition. Lull, in 1936,²⁴ and again in 1940,²⁵ reported on additional Pomeroy sterilizations bringing the total in the literature up to 812. All these cases were carefully followed. There were no known failures. In 1941, Thornton²⁶ reported 219 Pomeroy sterilizations and a high follow-up rate. Lock,²⁷ in 1942, reported on 57 additional cases. In Table II, these reports are itemized, including our 174 Pomeroy sterilizations. The incidence of failure for this procedure is half of that for the Madlener.

Indications, Methods, and Results

On the obstetric service at the Sloane Hospital for Women, between January, 1934, and January, 1944, 233 tubal sterilizations were performed. Of these,

174 or 75 per cent were Pomeroy resections, with one failure. Other procedures used included 42 cornual resections, comprising 18 per cent, with no failures, and 14 (7 per cent) segmental resections with or without burial of the stumps. There was one failure in this latter group. The two failures will be discussed later. All sterilizations were performed at the time of cesarean section, in conjunction with hysterotomy or as puerperal procedures.

During this ten-year period there were 612 cesarean sections. Of these, 102 were accompanied by tubal sterilizations, giving an incidence of 16.6 per cent. Seventeen and six-tenths per cent of these sterilizations were performed

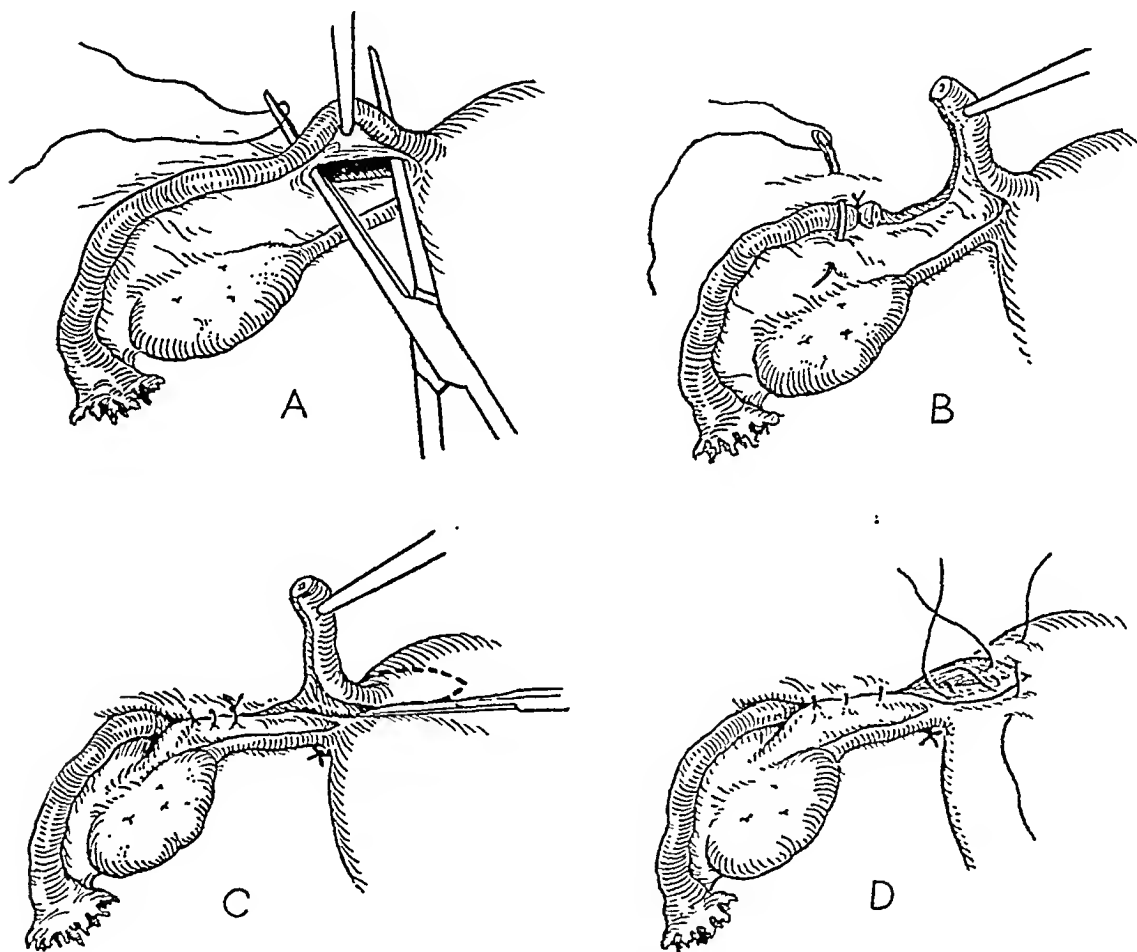


Fig. 2.—Cornual resection.

TABLE II.—REPORTED SERIES OF POMEROY STERILIZATIONS

AUTHOR AND DATE	NUMBER OF CASES	NUMBER OF FAILURES	PER CENT
Lull ²⁵ 1940	812	0	0
Thornton ²⁶ 1941	219	0	0
Lock ²⁷ 1942	57	2	3.5
Sloane 1944	174	1	0.6
TOTALS	1,262	3	0.31

at the time of the first cesarean; 53.9 per cent at the time of the second cesarean, and 28.4 per cent at the time of the third cesarean. Based on an eight-year survey, our secondary cesareans are one-third as numerous as the primary sections, and tertiary sections are one-fourth as numerous as the secondary sections.

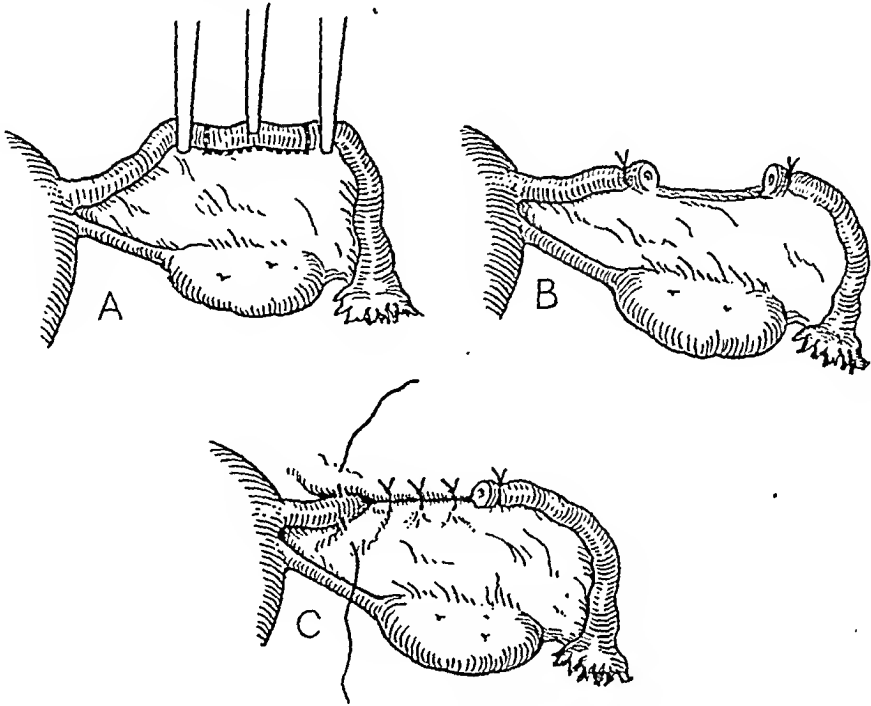


Fig. 3.—Segmental resection as performed by Dr. B. P. Watson.

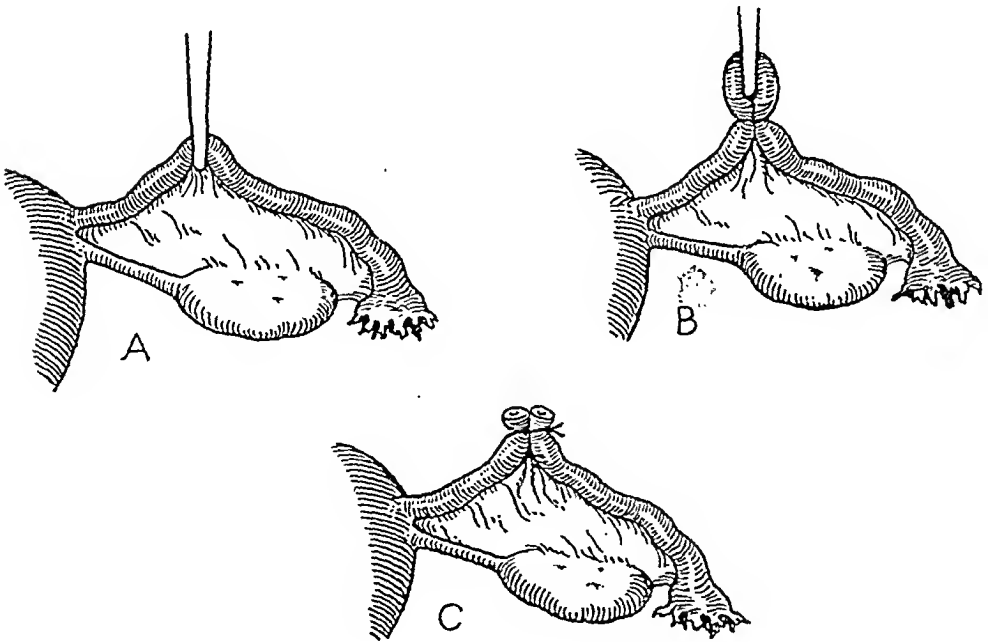


Fig. 4.—The Pomeroy sterilization.

Accordingly, we perform tubal sterilizations on approximately 6 per cent of our patients at the time of their first cesarean, 40 per cent at the time of their second cesarean, and 80 per cent at the time of the third section.

TABLE III. INDICATIONS FOR STERILIZATION AT PRIMARY CESAREAN SECTION

Rheumatic heart	3
Pre-eclamptic toxemia	2
Chronic glomerular nephritis	1
Previous vaginal plastic	2
Syphilitic aortitis	1
Chronic pulmonary tuberculosis	2
Intracranial tumor	1
Cicatrix of cervix	1
Psoas abscess	1
Multiparity (associated with one of above indications)	6

The indications for sterilization at the primary cesarean are shown in Table III. The indications for cesarean section were obstetric in each instance. The indications for sterilization were primarily medical. Several patients were multiparas (three or more living children), who required a section because of placenta previa.

The techniques used for sterilization in this group were as follows:

Pomeroy resection—(77.4 per cent)	79
Cornual resection—(13.7 per cent)	14
Segmental resection—(7.8 per cent)	8
Salpingectomy—(1 per cent)	1

One failure occurred in the group of segmental resections. This patient was a primipara with an asymmetrical pelvis and an active tuberculous hip. She became pregnant within six weeks after an uneventful postoperative course. At the secondary cesarean section the left tube appeared to be intact. There was superficial scarring in the isthmic region of the tube. The left ovary contained a corpus luteum. Only the distal portion of the right tube could be identified. A complete left salpingectomy and right cornual resection were performed.

Of these 102 patients, only 9 could not be followed. The average follow up for the entire group was 18.5 months apiece. There was no maternal mortality. Postoperative complications included one pulmonary embolus, one thrombophlebitis, and one wound infection.

During the same ten-year period, 97 abdominal hysterotomies and sterilizations were performed. All of these patients were young individuals with valid medical indications for both termination of their pregnancies and sterilization. All patients were at least three months pregnant and therefore were not considered suitable candidates for dilatation and curettage. In each instance it seemed desirable to preserve the menstrual function. The indications are itemized in Table IV. About 50 per cent of these patients were multiparas (three or more living children). There were no known failures. Four patients could not be followed. The average follow-up for the entire group was 29.5 months per patient.

There was one maternal death. This patient had an intracranial tumor. She died on her fourth postoperative day from peritonitis and abscess of the uterine incision.

The types of operation used in this group were as follows:

Pomeroy resections—(65 per cent)	63
Cornual resections—(28.7 per cent)	28
Segmental resections—(6.3 per cent)	6

TABLE IV. INDICATIONS FOR ABDOMINAL HYSTERECTOMY AND STERILIZATION

Rheumatic heart disease	28
Psychoses	9
Chronic glomerular nephritis	6
Active pulmonary tuberculosis	5
Diabetes mellitus	4
Hypertensive cardiovascular disease	8
Recurrent eclampsia	5
Hyperthyroidism	2
Familial insanity	1
Syphilitic aortitis	1
Syringomyelia	1
Chronic encephalitis	2
Recurrent hyperemesis	1
Tertiary syphilis	1
Essential hypertension	2
Ventricular extrasystoles	1
Aneurysm of aorta, syphilitic	1
Epilepsy	3
Chronic pyelonephritis	4
Lymphoma of nasopharynx	1
Carcinoma of thyroid	1
Brain tumor	3
Hypothyroidism	2
Moron	1
Hydronephrosis	1
Multiple sclerosis	2
Carcinoma of breast	1
Bilateral ureteral strictures	1
Thrombophlebitis	1
Bronchiectasis	1
Splenomegaly	1
Multiparity	45

A small group of 34 postpartum sterilizations were performed. The Pomeroy resection was used exclusively. There was one failure. This patient was a rheumatic cardiac who was sterilized after the birth of her third child. She returned pregnant nine months after discharge. A complete abdominal hysterectomy was performed. At laparotomy, the right tube appeared to be intact. The isthmical portion was slightly scarred. There was a gap in the left tube at its middle third, approximately 2 cm. in length.

Discussion

Any procedure designed to prevent conception in a woman in the child-bearing age must not be considered casually. The prevalent attitude toward such procedures at the Sloane Hospital for Women has been well stated by Watson.²³ The indications for such operations need no further comment.

There are few figures quoted in the literature which offer a basis for comparison with ours in terms of the incidence of sterilizing operations on obstetric patients. Lull's²⁴ statistics are quite comparable to ours.

Lull's Nine-Year Survey

14,039 obstetric patients
Total number sterilized, 223 (1.3 per cent)
Sterilized at cesarean, 111
Sterilized at hysterotomy, 19

Sloane's Ten-Year Survey

16,266 obstetric patients
Total number sterilized, 233 (1.4 per cent)
Sterilized at cesarean, 102
Sterilized at hysterotomy, 97

In terms of viable births we sterilize 0.83 per cent of our obstetric patients.

Four techniques for tubal sterilization have been described. Practically every method of tubal sterilization described in the literature is based on one of these operations, with one or more minor individual variations. The fact that there are so many variations reported indicates that none has been entirely successful. Undoubtedly an important cause of failure in many of the reported cases was faulty surgical technique. This was unquestionably the cause of failure in our two cases. In each instance, the resection was apparently performed at the rather fixed isthmical portion of the tube and evidently only a tiny fragment of tube was excised. Apparently in both cases the divided ends of the tubes readily adhered to one another and rapidly recanalized after absorption of the ligature. However, after studying these different operations and the causes of failure in each, certain biologic and mechanical factors are encountered which indicate inherent weakness in many of these procedures. Rubovits and Kobak,²⁹ and Dippel³⁰ have had the opportunity of making serial sectioning of tubes of individuals on whom the Madlener sterilization had been performed unsuccessfully. These authors clearly demonstrated the occurrence of the biologic phenomenon which Sampson called endosalpingiosis. Sampson studied by serial section both the tubes and cornual regions of uteri of individuals who had been subjected to tubal sterilizations and total salpingectomies. He demonstrated the great propensity of tubal epithelium to regenerate and recanalize adjacent fiber-muscular tissue following injury. Of 147 cases studied, only 35 showed evidence of normal tubal healing. Rubovits and Kobak,²⁹ and Dippel³⁰ have demonstrated the presence of tuboperitoneal fistulas and canalization of the mesosalpinx following the Madlener operation. The mechanical factors concerned in the carefully studied failures seem to be related to the use of nonabsorbable suture material which is notorious for its ability to cut through both devitalized and normal tissue. It appears, then, that the Madlener operation may be justly criticized as unsound from both the mechanical and biologic aspects. A survey of the literature reveals a relatively high incidence of failure of this operation to fulfill its purpose. The high incidence of failure for this technique may be demonstrated by lipiodol studies as suggested by Rubovits and Kobak,²⁹ and Lull.²⁴

Cornual resection does not seem to be as popular today as it was ten years ago. This operation is an elaborate procedure requiring more operating time and very careful approximation of tissues. It is a notoriously bloody operation. The failures of this procedure, apparently, have been due to small hematomas and foreign body reactions resulting in one or more fistulas communicating with the peritoneal cavity and lined by tubal epithelium. At Sloane we have completely discarded this operation.

Burial of one or both tubal stumps following a segmental resection has not been found to be foolproof. Sampson³¹ believes that this refinement increases the blood supply to the injured tubal epithelium and thus abets the rapid regeneration of the tubal epithelium with the formation of fistulas.

An analysis of the Pomeroy operation indicated that it avoids these various pitfalls. From the *most mobile portion* of the tube, a segment about $1\frac{1}{2}$ to 2 inches is excised after ligation with fine absorbable suture material. No crush-

ing is employed. The tiny fragments of tube, distal to the ligature following excision, become necrotic and absorbed. Just beneath the ligature each end of the tube becomes sealed off by peritoneum, inasmuch as the muscular wall retracts slightly. Following absorption of the ligature, the two ends of the tube retract for a distance of 2 to 3 inches. Thus the continuity of the tube is completely interrupted. The drawing in Fig. 5 was made from an autopsy specimen of one of our patients who died three months after an abdominal hysterotomy and Pomeroy sterilization for subacute bacterial endocarditis. Lull²⁵ and Goldblatt³² have had the opportunity of observing the end result of this operation at subsequent laparotomies and describe the same findings. Unfortunately our specimen did not yield microscopic sections of sufficiently good quality for microphotographs because of faulty fixation.

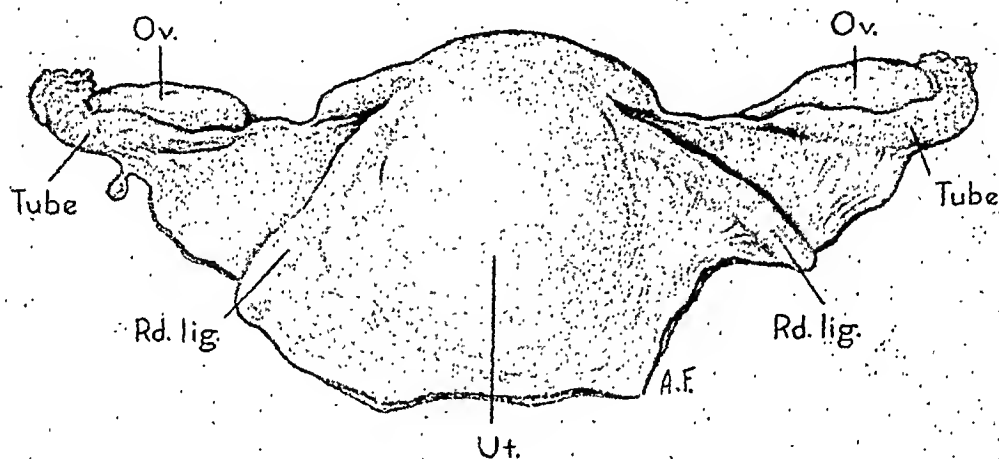


Fig. 5.—Drawing of autopsy specimen three months following Pomeroy sterilization. Note the wide retraction of the ends of the tubes and completely peritonealized surfaces.

How long a patient should be followed after a tubal sterilization is difficult to state. The majority of failures become manifest within three to six months after the original procedure. However, a latent period for as long as ten years has been recorded in the German literature. Of interest, also, is the possibility of development of a tubal pregnancy. The majority of such complications reported appear to have followed the Madlener operation.

Summary

Two hundred and thirty-three tubal sterilizations performed during a ten-year period have been reviewed.

The literature pertaining to tubal sterilizations has been reviewed in an effort to determine which type of operation offers the highest incidence of success.

Conclusions

1. The Pomeroy sterilization is a safe, simple, sure, and rapid procedure.
2. The reported failures of this operation are 50 per cent fewer than for the Madlener sterilization.

3. The Pomeroy sterilization avoids mechanical and biologic hazards to success, inherent in other types of tubal sterilization.

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EARLY CONTROLLED AMBULATION IN THE PUERPERIUM*

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THE period for ambulation of obstetric patients for many years has aroused considerable differences of opinion.

White of Manchester, England, 1728-1813, stated "as soon as the patient gets out of bed the better and this should not be deferred beyond the second or third day at the furthest."¹

In 1820, Gooch cautioned that patients should be kept in bed for three weeks after delivery because of the danger of prolapse of the uterus. Between this era of obstetrics and the present era, the period of ambulation has varied from one extreme to the other. It is the purpose of this treatise to record the gross data of a large group of patients under controlled ambulation and a detailed report of a smaller group of private patients, to show that the advantages of controlled ambulation may be obtained without incurring any of the disadvantages in the puerperal woman.

Repeated experience with the difficulty of keeping in bed throughout the early puerperium large numbers of Negro patients delivered at home first called our attention to the possibility of early controlled ambulation in obstetrics. This experience was further accentuated when construction of new facilities reduced the bed capacity of the obstetric service of Charity Hospital of New Orleans for a period of two years. Because of this fact it became necessary to send patients home by the fifth day and to allow them freedom of controlled ambulation. Observation at the six weeks' examination of these patients revealed no apparent differences in abnormalities as contrasted with the previous years when the patients had been maintained at absolute bed rest with exercise.

In 1940, with this experience as a background, a system of early discharge of the puerperal patient from the third to fifth day under controlled ambulation was instituted. There was a careful daily follow-up in the homes by the nursing service of the Maternal and Child Health Division of the City Board of Health of New Orleans. The initial survey of 2,926 of these patients revealed the fact that only 30 developed immediate puerperal complications.² These were in the nature of two cases of endometritis, two of mild pyelonephritis, and twenty-six with engorgement of the breast and/or fissured or cracked nipples.

Postpartum examination of these patients at six weeks revealed that the general recovery rate was better in comparison to those cases that remained nonambulatory in the hospital. Relaxations and/or uterine prolapse, malpositions of the uterus, and subinvolution of the uterus were present in a smaller number than in nonambulatory cases.

A further detailed study of 323 private cases was undertaken in order to assay the advantages or disadvantages in a class of patients usually seen in private practice. These patients are not as hearty individuals as most of the patients seen in teaching institutions even though they are probably in a better state of general health.

*Presented before the Scientific Faculty of Southwestern Medical College.

Method of Ambulation

The criterion for allowing ambulation is that the patients are medically in a condition to be allowed this privilege.

The patient is advised to move freely in bed immediately upon recovery from whatever type of anesthesia may have been given. Every eight hours for the first twenty-four hours following delivery she is asked to sit up on the side of the bed for a few minutes, to cough vigorously to clear the respiratory system of any mucus and to stimulate the circulation in lower extremities. At each voiding the patient sits upright on the bedpan. On the second day the patient stands upright on four different occasions for a few minutes, followed by sitting upright in the chair for a period of fifteen to twenty minutes. Voiding is accomplished while sitting on the bedpan placed on a chair. On the third day ambulation about the room for short periods of time on three or four different occasions is permitted. Complete bathroom privileges are granted. Thereafter, controlled ambulation is permitted with the restriction that each hour of ambulation be terminated by an hour of bed rest. By the tenth day the patient is completely ambulatory, requiring only intermittent periods of rest. At the end of the twenty-first day the patient is allowed to resume complete outdoor ambulation without unduly tiring herself.

Clinical Material

There were 227 primigravida cases and 96 multigravida, the latter varying from gravida ii to vii. The duration of labor in the primipara averaged 12 hours, 32 minutes; and the multipara, 7 hours, 18 minutes. There were 318 vertex and 5 breech presentations. Labor was terminated in 285 instances by the application of outlet forceps, in 7 instances by the application of midforceps, and in 5 instances by the use of Piper forceps for the aftercoming head following 3 spontaneous breech deliveries, and 2 breech deliveries by manual aid. Twenty-six cases delivered spontaneously.

Sedation of varying degrees was employed in all cases using nembutal and scopolamine. Delivery was accomplished in 103 cases under caudal analgesia; 30 cases under local pudendal block; and 190 cases with gas anesthesia. Left mediolateral episiotomies were performed in 290 cases and repair accomplished using chromic 000 interrupted sutures. Twenty cases were delivered without episiotomies. In three of these, first-degree lacerations occurred.

The third stage of labor was managed by the administration of ergonovine, $\frac{1}{320}$ grain, intravenously, with delivery of the anterior shoulder in other than caudal analgesia cases. In the latter it was given after delivery of the placenta. In three instances more than average bleeding occurred at this period.

Results

Immediate Puerperium (Two Weeks)

General.—In all instances patients expressed the opinion that a general feeling of well-being occurred from the ambulation. This was particularly true in the multigravida who felt that recovery was hastened by ambulation in comparison to their previous puerperium.

Lochia.—There was the greatest drainage of lochia in the first three to five days with a rapid decrease in the amount until almost complete cessation by the tenth day when the lochia was completely serous.

Bladder and Bowel.—In not a single instance was catheterization necessary. Bowel function was normal without the use of enemas or cathartics. It was noted that the patients complained less of hemorrhoids than had been observed previously in nonambulatory patients.

Uterus.—In all but six instances involution of the uterus was accelerated, and the fundus by the seventh day was palpable between the symphysis and two fingerbreadths above it. By the tenth day the uterus was no longer palpable, being in the pelvis. The six cases which underwent slower involution exhibited a palpable uterus at the symphysis between the tenth and twelfth days, it being in the pelvis by the fifteenth day.

Episiotomy.—Complete healing was present by the seventh day in all except two instances in which dehiscence of a moderate degree was present, so that healing occurred by secondary intention in these two cases by the twelfth day. There was a notable lack of complaint about episiotomy pain after the first day of ambulation.

Morbidity.—In ten cases morbidity was present for an average of three days. Etiology of such morbidity was pyelonephritis in two cases, endometritis in three, and mastitis in five cases.

Postpartum Bleeding.—In six cases bleeding was exaggerated enough to require a short course of oxytocics. There was present no immediate severe bleeding.

Pulmonary and Vascular Complications.—None were present.

Delayed Puerperium (Six Weeks)

General.—All patients when questioned had been completely ambulatory from the twenty-first postpartum day without any evidence of general fatigue but with a state of well-being.

Uterus.—Subinvolution was present in four cases to the extent that the uterus was twice its normal size at this period. Retroposition of the uterus was present in sixteen instances. There was an absence of relaxation of the anterior and posterior vaginal walls and of uterine prolapse at this time.

Pulmonary and Vascular Complications.—None were present.

Delayed Puerperium (Six Months)

One hundred fifteen of the above patients were re-examined at this period. The patients again reiterated their satisfaction for their rapid return to normalcy without any discomfort to them. There was an absence of any additional abnormality as compared with the six weeks examination. Particular reference to the possibility of relaxation and/or prolapse revealed nothing of note.

Discussion

In advocating early controlled ambulation during the puerperium one should be cognizant of its potential advantages and disadvantages.

The potential disadvantages expected (postpartum hemorrhage, excessive relaxation and/or uterine prolapse, and dehiscence of episiotomy) were less in these series than in previous series of nonambulatory patients. True, complete elimination of prolapse and/or relaxation as a complication requires a longer follow-up than in these series. However, if deliveries are accomplished in a manner to avoid injury of the fascia propria, there should be no increase in relaxation and/or prolapse. When injury to the fascia propria has occurred, it is not conceivable that bed rest produces a return of fascial support. In the past the obstetric patient has remained nonambulatory for long periods of time, yet large numbers of cystocele, rectocele, and uterine prolapse are seen in gynecologic clinics.

The advantages obtained from controlled ambulation of these two series were beyond any expectation. There was a complete absence of bladder and bowel disturbances, phlebothrombosis and thrombophlebitis, with a marked reduction in uterine subinvolution and retractions. The obtaining of these advantages without the appearances of the expected disadvantages makes one realize that controlled ambulation has much to offer the obstetric patient.

Conclusions

A gross report of 2,926 cases and a detailed report of 323 cases who experienced early controlled ambulation is given. Early controlled ambulation is shown to offer advantages to the obstetric patient without imposing any disadvantages.

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THE ANESTHETIC MANAGEMENT OF PATIENTS WITH RESPIRATORY PARALYSIS REQUIRING LAPAROTOMY

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IN A COMPANION publication,¹ the obstetric and surgical management of a patient who underwent laparotomy for cesarean section is reported. The special interest in the case was the complicating acute anterior poliomyelitis which had produced complete paralysis of the respiratory muscles. The present discussion considers the anesthetic management of the same patient. During operations under similar circumstances which have been reported, local anesthesia was utilized while artificial respiration was employed.^{2, 3} In one instance, the baby survived six hours and in the other, the mother lived two days. Anesthesia was reported as satisfactory.

The pregnancy of the 27-year-old subject of this report was further complicated by breech presentation, pyelonephritis, and acute glomerulonephritis. The patient had overflow incontinence and was unable to defecate. All voluntary motor function of spinal innervation was lost except a very limited motion of the right hand. The cough reflex was absent and there was some facial paralysis. Any passive movement caused severe pain. Anesthesia was complicated further by prematurity (thirty-five weeks' gestation).

Selection of Agent

The anesthetic gases, the volatile agents, the intravenous drugs and the local or regional agents of current popularity have given satisfactory results when competently administered during cesarean section. The absolute contraindications to the use of any of these agents for the subject of this report were few. The existing nephropathy was considered a logical reason for avoiding ether or chloroform and to a lesser extent the intravenous barbiturates. The desire to minimize postanesthetic nausea and emesis, which may be a serious complication for a respirator patient without a cough reflex, added further reasons for not employing volatile agents. The choice of the agent was then limited to the gases, the intravenous and the local agents. Consideration was given to the one of these that could be adapted most conveniently to the technique required. Artificial respiration was essential during the entire period that the patient was to be outside the respirator. Although this could be accomplished conveniently by the anesthetist with comfort for the patient, it was thought inadvisable to prolong it for any reason, particularly if the patient was to remain conscious. Since the techniques with local infiltration, regional nerve block (caudal), and spinal anesthesia required more time, they seemed less desirable. A further factor in not choosing one of them was the intense pain caused by any passive motion.

Although the amount of an intravenous drug such as pentothal sodium would probably have been small for a relatively short procedure to be completed for a patient with paralyzed musculature, an evaluation of the effects of this drug on the fetus is still a subject of controversy. Furthermore, the drug is detoxified and eliminated by the body and the physical condition of this patient opposed any additional burden of detoxification and elimination of drugs. In addition, the undesirable necessity of dividing the responsibility of artificial respiration and anesthesia when intravenous injections are employed, inclined us to favor inhalation anesthesia.

Nitrous oxide, ethylene, and cyclopropane have many advantages in obstetric surgery. The less potent agents, nitrous oxide and ethylene, have been declared dangerous frequently because of the low oxygen concentrations used when they are administered. The justification of this criticism lies not in the agents but in the faulty technique usually employed. To use these gases safely during laparotomy for an unpremeditated patient, even though relaxation is not a consideration, requires an exacting, deliberate technique. When continuous artificial respiration is a primary essential, the procedure may become more complicated and multiply the chances of technical errors. Because cyclopropane is more potent, the danger of low maternal or fetal oxygen saturation is diminished. It may, however, influence the incidence of asphyxia neonatorum. When its administration is prolonged or profound narcosis is produced, the respiratory function of the infant may be somewhat depressed. The rapidity with which light surgical anesthesia is produced permits prompt surgery and, when delivery can be accomplished within a few minutes (12 to 15), the concentration of the gas in the fetal circulation is negligible and ineffective.⁴ Since the convenience of cyclopropane administered during continuous artificial respiration is not surpassed by any other agent given by inhalation, it was the optimum choice.

Anesthetic Technique

Although the techniques for modern anesthesia may seem complicated, most of the procedures are performed without serious risk. The present development of surgery has required the addition of more elaborate appliances and a more versatile approach to the problems presented. The anesthetist has long since accepted the responsibility of assuming certain functions of the anesthetized patient. He confidently expects to control the patient's breathing during many surgical manipulations. When this is necessary throughout the procedure because of respiratory paralysis, no serious obstacle to safe, convenient anesthesia is added. Controlled respiration is more easily performed when a functioning airway is assured with an endotracheal catheter in place. Such airways may be inserted with only slight discomfort to a conscious patient if the upper air passages and the proximal area of the trachea are anesthetized by spraying a suitable anesthetic solution through the nares and mouth. Airways may be placed, then, either through the nostril, blindly, or with slight discomfort by direct vision with a laryngoscope. Endotracheal airways may be inserted conveniently after anesthesia has been induced. If surgical anesthesia is to be

continued, there is no need to anesthetize the upper air passages with local anesthetic solutions.

Controlled respiration in the anesthetized patient is performed simply and satisfactorily by using a well-fitted face mask and a rebreathing bag with a carbon dioxide absorbing unit in the system or a properly adjusted exhalation valve. Pressure, sufficient to hyperventilate the lungs modestly, is then applied to the breathing bag during the inspiratory phase of respiration. Tissue carbon dioxide is thereby reduced and, after a variable time, the amount will be insufficient to reach the threshold of a respiratory center depressed by anesthesia. This may be continued as desired.

Conduct of the Case

The patient was fully aware of an impending operation of dramatic and uncommon seriousness. She was entirely cooperative although, naturally, apprehensive. It was extremely important that those who were to treat her, particularly until she was asleep, should have her confidence; therefore, visits were made before the day of operation, the procedure discussed, and a friendly and reassuring environment established. She was removed from the respirator for short periods on several occasions to demonstrate to her that she was safe and comfortable when the resuscitator* was used.

Preanesthetic medication was not given, in order to avoid any effects upon the fetus. The initial procedure was the anesthetization of the upper air passages with an aqueous solution of cocaine (2 per cent). This was applied with a common atomizer by spraying in each nostril and over the root of the tongue as the respirator produced the inspiratory phase of respiration. After ten minutes, endotracheal intubation was attempted with a soft rubber airway directed blindly through a nostril. The attempt was soon abandoned since the head could not be adjusted without releasing the respirator attachments about the neck. The patient was then given cyclopropane-oxygen anesthesia for two minutes and a spring-wire latex-covered airway was introduced under direct vision with a laryngoscope. Anesthesia was not continued. The patient recovered at once and was pleased that she now had experienced going to sleep and awakening from cyclopropane. With the resuscitator adjusted, the patient was transported to the operating table and put in position. Asepsis was applied, drapes put in place, and the surgeons made ready to operate. The resuscitator was then discontinued and a mask and bag were utilized to supply the cyclopropane-oxygen mixture as respirations were manually controlled. The stage of surgical anesthesia was obtained within three minutes and was maintained in light first plane throughout the operation. The baby was delivered four minutes after surgery had been started. It cried lustily and spontaneously a few seconds after removal from the uterus. The operation was completed in twenty-five minutes, at which time anesthesia was discontinued, and the resuscitator put into use again. The patient was fully awake and rational four minutes after anesthesia had been discontinued.

*An adult model Kreiselman resuscitator.

During the procedure, there were minute-to-minute determinations of the pulse rate and blood pressure. The latter varied from 180/140 to 110/90, being 160/90 at the start and 150/90 when anesthesia was concluded. The pulse rate was 110 at the beginning of induction and remained rapid throughout. It was noted with interest that the pressure required to inflate the lungs became markedly reduced after the baby was delivered.

Discussion

The refinements of modern anesthesia have armed the anesthetist with many means to minimize the danger and discomfort to the patient and provide reasonable convenience for the surgeon during any manipulation justifiably indicated. There are minor differences among anesthetists in evaluating drugs and techniques, and individual preferences are not uncommon. All are agreed, however, that if gross errors in judgment are excluded, the success of anesthetic procedures depends to no small extent on the technical proficiency exercised. Those entrusted with the anesthetic management of the subject of this report were familiar and experienced with the drug and the method. There was complete confidence in its success and there was no incident during the procedure to indicate that such confidence was unjustified. A similar method would be employed if we should encounter another patient presenting the same problems. Unless another condition is present as a contraindication to the use of cyclopropane, the method seems to be applicable whenever laparotomy needs to be performed for a patient with respiratory paralysis.

Summary

The anesthetic management of a patient with acute anterior poliomyelitis and respiratory paralysis who required cesarean section is described.

Cyclopropane-oxygen was given by a mask and rebreathing bag which also served as a vehicle for continuous controlled respiration by manual pressure on the bag. An endotracheal airway was utilized.

Anesthesia was uneventful and the results entirely satisfactory.

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477 FIRST AVENUE
755 OCEAN AVENUE

PREGNANCY IN CASES OF PITUITARY DWARFISM

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THE pregnant dwarf is an obstetric problem which has received insufficient attention. Publications which have appeared have evidently been written with the idea of presenting an obstetric curiosity. This is unfortunate, for these people seem to be quite capable of becoming pregnant without difficulty. They present three very definite problems: The first is the consideration of the heredity of the physical abnormality and whether pregnancy should be advised or discouraged. The second is the character of the antepartum course. The third is the management of the labor. There are also the psychological complications which may arise from mother-child relationships, but these will not be discussed here.

A partial review of the available literature from 1901 to 1942 was made and is summarized in Table I, where the authors, with their cases, appear in chronological order.

In order to answer the first problem, it is necessary to divide dwarfs into two major types: the true dwarf and the achondroplastic dwarf. From the cases reviewed, it appears that the true dwarf was invariably the offspring of normal parents and in all cases gave birth to normal offspring. In the series of cases analyzed, there were three instances of true dwarfs^{4, 9, 10} and the offspring of each was found to be normal regardless of whether or not both parents were dwarfs. In only one case¹⁰ was the physical status of the father noted, and he also was a true dwarf. In addition to these, Gould and Pyle¹⁵ cite several other cases, and in each, the offspring was normal. They report that in 1742 Robert Skinner and his wife, both midgets, produced fourteen normal children, and in 1739, Joseph Browilaski, a midget, and his normal wife produced two normal children.

The achondroplasties, however, present a far different picture. Although an achondroplastic may be born of normal parents, the offspring of achondroplasties are very often born with the same affliction. In the series of cases presented, there were 15 achondroplastic mothers who bore 8, or 53.5 per cent, achondroplastic babies. It is apparent, then, that there must be an hereditary factor in achondroplasia which is lacking in the pituitary dwarf. Therefore, achondroplasties should be so advised when they seek premarital or obstetric advice.

As far as the antepartum course of either type of dwarf is concerned, there was very little to learn from their case histories to suggest that they fared any differently than other women. There may be psychological difficulties as were encountered in the case to be reported; for, although this patient was accustomed to the curiosity of the world about her, she had to be protected from the realization that, in her pregnant state, this curiosity would become unbearable. Since, in all cases, the pelvis were markedly contracted, an elective cesarean section was performed in each case. Thus, the management of labor will give rise to few complications if elective cesarean sections are performed.

AUTHOR	YEAR	TYPE OF DWARFISM	PELVIMETRY				
			DIAG. CONJ.	INTER-SPINAL	INTER-CRISTAL	INTER-TROCIL.	EXT. CONJ.
MacLean ¹	1903	Achondroplasia	2.5 in.	6.8 in.	8.0 in.		6.4 in.
Cutler ²	1904	Quest. rachitic	7.5 cm.	19.0 cm.	23.0 cm.	28.0 cm.	16.0 cm.
Lepage ³	1904	Achondroplasia	5.7 cm.	21.0 cm.	24.0 cm.		17.0 cm.
Porak		Achondroplasia					
Baldwin		Achondroplasia					
Potocki	1893	Achondroplasia					
	1894	(same patient)					
	-	5th pregnancy					
Fabre ⁴	1906	Pituitary dwarf	7.0 cm.	23.0 cm.	25.0 cm.		
Hirigoyen ⁵	1907	Achondroplasia		17.0 cm.	20.0 cm.		
Risso ⁶	1909	Achondroplasia	4.5 cm.	17.0 cm.	18.5 cm.	12.0 cm.	8.0 cm.
Fieux ⁷	1914	Achondroplasia	8.0 cm.	21.0 cm.	20.0 cm.		16.0 cm.
Clarke and Koenig ⁸	1923	Achondroplasia	6.0 cm.	21.0 cm.	23.0 cm.	31.5 cm.	17.0 cm.
McClaran ⁹	1924	Pituitary dwarf					
Mason and Turner ¹⁰	1928	Pituitary dwarf					
Young ¹¹	1934	Achondroplasia					
Balasquide ¹²	1935	Achondroplasia	6.4 cm.	18.0 cm.	20.0 cm.	21.5 cm.	17.0 cm.
Lemaire ¹³							
Mother	1892	Achondroplasia					
	1894						
	1905						
	1906						
	1910						
Daughter*	1934	Achondroplasia					
Spaling ¹⁴	1942	Achondroplasia	7.5 cm.	22.0 cm.	21.0 cm.	34.0 cm.	14.0 cm.
		Achondroplasia	9.5 cm.	22.0 cm.	23.0 cm.	31.0 cm.	17.0 cm.

*Daughter one of the five children noted above.

The case to be reported is that of M. N., a 41-year-old primigravid white pituitary dwarf, single, who presented herself for the first time at Bellevue Hospital on March 20, 1944. The patient's parents were both normal. Her father was 6 feet, 1½ inches tall, and her mother was 5 feet, 2 inches tall and weighed over 200 pounds. Her mother had eleven children: eight, including the patient, by a first marriage, and three by a second marriage. All siblings were normal, one brother being over 6 feet tall. There was no history of dwarfism anywhere in the family. The patient did not know when she first started to walk or talk, but believed these events occurred at normal times. She stated that she stopped growing at the age of four years. She went through the second grade of school at the age of 10 years and then "joined the show world."

She first started to menstruate at the age of 18 years and had a period every month lasting for four to five days, using 4 pads daily. There was no dysmenorrhea. After 1936, her periods began to occur every two months. Her last menstrual period was thought to have occurred on June 2, 1943. The date of conception was not known. The putative father was 29 years of age and normal in size. Nothing else could be learned about this man.

When the patient was first seen, she was complaining of abdominal pain. She was admitted to the gynecologic service where the diagnosis of intrauterine gestation was made and confirmed by x-ray. Shortly after, the patient was discharged and referred to the prenatal

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TYPE OF DELIVERY	RESULT OF BABY	REMARKS
Elective cesarean section at term. Sterilized	6¼ lb. normal male child	Patient's family normal
Cesarean section after onset of labor	Normal male child	Sister mentally retarded and an idiot cousin
Classical cesarean section 3 weeks before term	Achon. female, 2,550 Gm.	Patient's family normal
Cesarean section	Achondroplastic	Normal husband
Cesarean section	Achondroplastic	Normal husband
Cesarean section	Achon. female	Normal husband. Patient died from peritonitis following 5th pregnancy
Cesarean section	Achon. male	
Cesarean section	Normal female	
Cesarean section after onset of labor	Normal baby	Patient's family normal
Classical section after onset of labor	Normal female, 2,850 Gm.	Patient's family and husband normal
Elective cesarean section	Normal premature infant	Patient's family normal
Elective classical section	Normal male, 3,300 Gm.	
Cesarean section after onset of labor	Achon. male, 7 lb.	Patient's family normal
Cesarean section after onset of labor	Normal male, 7½ lb.	Patient's family normal
Cesarean section after onset of labor	Normal baby, 7 lb.	Patient's family normal, husband—pituitary dwarf
Elective cesarean section	Unknown	
Cesarean section after onset of labor	Normal male, 5¼ lb.	Patient's family and husband normal
Classical cesarean section	Normal baby	Baby died at 2 mo.
Classical cesarean section	Unknown	
Classical cesarean section	Twins	1 died at 1 yr.; 1 died at 1 wk.
Classical cesarean section	Achon. female, 3,345 Gm.	
Porro	Unknown	Baby died
Classical cesarean section	Normal male	Same person
Low cervical cesarean section after onset of labor	Achondroplastic male	Patient's family normal
Cesarean section after onset of labor	Normal male	Patient's family normal

clinic, but, within a few days, sought readmission for the same complaints. This time, she was sent to the obstetric ward. There was no organic cause for this pain, for after she had become acclimated to her surroundings and realized that fellow patients, nurses, and medical staff were sympathetic, her complaints vanished. However, whenever she felt that she was not being given enough attention, her complaints would recur. Her exacerbation of pain and immediate response to sympathetic attention and sterile saline hypodermic injections followed an infantile behavior pattern. She was often childish in her expressions and activity, and spent much of her time cutting paper dolls.

The patient was 42 inches tall and normally weighed about 61 pounds. On April 10, 1944, her weight was 70 pounds and two months later, at the time of delivery it was 76¼ pounds. She never presented signs or symptoms of toxemia. Although her body features were small, her external genitalia were well formed. Her bony pelvis, however, was definitely small. By x-ray, the pelvis was found to be platypelloid in character. The anteroposterior diameter of the inlet was 7 cm., the transverse diameter 9.5 cm., and the interspinous diameter 7 cm.

Since the last menstrual period and expected date of confinement were not definite, and the baby was small, it was decided to keep the patient under observation and perform a cesarean section just as soon as she went into labor. On June 3, 1944, at 8:00 A.M., spontaneous labor began. The baby was estimated at 4½ pounds and the vertex was floating. The

patient was taken immediately to the operating room where a low flap cesarean section under local anesthesia was performed without difficulty.

The baby was a female, weighing 4 pounds, 15 ounces, and measuring 16 inches in length. Unfortunately, the baby had multiple congenital deformities and died three hours after delivery. An autopsy disclosed the following abnormalities: meningocele, polydactylism, congenital polycystic kidneys, congenital cystic liver, cor biloculare, atresia of urinary bladder, split tongue, prematurity, and partial expansion of lungs with congestion and hemorrhage. No instances were encountered in the literature of babies born of pituitary dwarfs with congenital anomalies of this type.

The patient ran a nonmorbid postoperative course which, except for a mild infection at the site of a tension suture, was uneventful. She was discharged on the twenty-fifth day in good condition.

Conclusions

1. From the available literature, the true dwarfs seem, invariably, to give birth to normal babies.
2. Achondroplastic dwarfs frequently give birth to achondroplastic babies, indicating the presence of an hereditary factor.
3. Achondroplastic dwarfs should be forewarned of the strong possibility of having an achondroplastic child.
4. True dwarfs can be told that their chances of having a dwarf child would be the same as that of normal individuals.
5. The antepartum course of a pregnant dwarf does not seem to be different from that of a normal individual.
6. Pregnancy in a dwarf should be terminated by an elective cesarean section.

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ETIOLOGY AND TREATMENT OF HEARTBURN OF PREGNANCY

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IT HAS often been said that the degree of our knowledge of any pathologic condition can be accurately measured by the number of remedies for the condition which are in current vogue. Usually the more remedies advocated for a disorder, the less is known about it. This is quite true in the case of heartburn, especially that variety associated with pregnancy.

Causative Factors

Interestingly enough, as Alvarez¹ has pointed out, heartburn rarely is associated with organic disease, which may be one reason for the lack of real interest in its treatment. However, the persistence of even a slight degree of heartburn will tend to lower the efficiency and morale of the pregnant woman; and if the condition is more severe and occurs at night, it might well interfere with sleep, and thus be a potential threat to the welfare and health of the patient.

There have been cited a great many possible causative factors, and treatment has been based upon these. One of the most commonly accepted theories is that popularized by Jones and Richardson.² They distended various portions of the esophagus in 29 patients by means of a small rubber balloon. No less than 19 of the patients complained of a hot, burning sensation when the lower third of the organ was distended. Furthermore, if quantities of acid, alkali, barium suspension, or even cold water were introduced through a tube, heartburn followed and was accompanied by spasm and reverse peristalsis of the region of the esophagus where the fluid had been given.

The acidity of the gastric contents was once thought to play a major role, but the work of Barsony and Szemzo³ and others^{1, 4} seems to have minimized its importance. As a matter of fact, during pregnancy when heartburn is very common, Strauss and Castle⁵ have shown that gastric acidity decreases as the pregnancy advances, and is at its lowest point during the third trimester, when the heartburn is most prevalent and severe. Obviously the use of alkalinizing agents such as sodium bicarbonate is completely without rationale.

Changes in the Stomach During Pregnancy

Although many additional theories as to the etiology of heartburn have been propounded, it is not within the scope of this report to list them all, but rather to concentrate on the most likely causative factors as related to the gravid state. Williams⁶ has summarized the changes in the stomach and its physiology during pregnancy. Normally the stomach lies in an essentially vertical position. However, as pregnancy proceeds, the enlarging uterus encroaches upon the abdominal organs and forces the stomach out of position. Thus, at or near term, the gastric fundus has been pushed up under the left leaf of the diaphragm and the axis of the stomach rotated about 45 degrees to the right. In addition, the greater curvature has been forced nearer the cardia. Such changes hinder the emptying of the stomach and tend to precipitate waves of reverse peristalsis.

There is also an increasing atony of the stomach musculature as pregnancy progresses. The cardiac sphincter, as well as the lower end of the esophagus, seem to be particularly involved in this process, thus permitting easy access of gastric contents into the distal esophagus. This may explain why heartburn during pregnancy is complained of more frequently when the patient is in a recumbent position; as a matter of fact, many patients have the distress only during the night.

A third major change in the physiology of the stomach during pregnancy is its diminished motility. Normally the emptying time of the stomach is about two hours, whereas in pregnancy this time may be doubled.⁷

Neuromuscular Theory

On the basis of the above-noted changes in the stomach during gravidity, we can readily understand the neuromuscular theory of heartburn. According to the proponents of this hypothesis, heartburn is the result of a regurgitation of gastric contents into the distal esophagus with its sensitive neural endings plus the intermittent spasm of the pyloric sphincter.

Williams⁶ actually demonstrated these suppositions with the aid of a barium meal and fluoroscopy. In the cases he studied he found no evidence whatsoever of any anatomic derangement other than those physiologic ones previously mentioned.

Treatment

With such a theory of disturbed neuromuscular function of the stomach and esophagus, it was rational⁶ to consider the use of prostigmine, a synthetic cholinergic drug, as a therapeutic agent. This drug has been shown both experimentally and clinically to have a very definite peristalsis-increasing effect on the intestinal tract.⁸⁻¹⁰ Since the esophagus and stomach are embryologically derived from the same tissue as is the intestinal tract, it seemed not unreasonable for Williams⁶ to experiment with prostigmine. He reported 16 cases of heartburn during pregnancy thus treated. Each patient was given 0.5 mg. prostigmine methylsulfate subcutaneously. In 14 instances relief was considerable or complete within twenty-four hours. Half of his cases reported a recurrence of symptoms within a week or ten days, but were again relieved with another injection of prostigmine.

Realizing that the condition occurs more often during the night or at other times when immediate access to the attending physician is not convenient or practicable, we decided to determine the value of prostigmine bromide tablets given by mouth.

Accordingly, 20 pregnant women complaining of heartburn were given a supply of prostigmine bromide tablets (15 mg. each), and instructed to take one as soon as the symptom appeared. Fifteen of the 20 patients reported complete relief within fifteen minutes after taking one tablet. If the symptom recurred (as it often did each day), another tablet of prostigmine bromide gave similar, prompt relief. Two patients reported partial relief; two obtained no benefit at all; and in one case the results were inconclusive (see Table I).

TABLE I

PATIENT	ONSET AND SEVERITY	DOSE FOR RELIEF	RESULTS
1. P. W.	33rd wk., severe at night	15 mg. p.r.n.	Immediate and complete
2. H. A.	30th wk., severe at 2 A.M.	15 mg. p.r.n.	Immediate and complete
3. F. C.	27th wk., after meals	15 mg. p.r.n.	Immediate and complete
4. I. C.	28th wk., severe at 2 A.M.	15 mg. p.r.n.	Immediate and complete
5. R. K.	24th wk., after supper	15 mg. p.r.n.	Immediate and complete
6. A. S.	29th wk., severe after meals	15 mg. (10 doses)	No relief
7. O. C.	27th wk., 10 P.M. with vomiting	15 mg. (2 doses)	No relief
8. H. N.	21st wk., severe after meals	15 mg. p.r.n.	Immediate and complete
9. F. G.	32nd wk., severe after meals	15 mg. p.r.n.	Immediate and complete
10. R. C.	12th wk., severe at 2-3 A.M.	15 mg. p.r.n.	Immediate and complete
11. S. B.	30th wk., mild after supper	15 mg. p.r.n.	One tablet at bedtime gave relief
12. J. R.	31st wk., severe	30 mg. p.r.n.	Delayed but complete relief
13. A. G.	36th wk., mild	15 mg. (3 doses)	Inconclusive
14. L. W.	34th wk., severe all day and night	30 mg. p.r.n.	Partial relief
15. N. McK.	27th wk., severe after meals	15 mg. p.r.n.	Immediate and complete
16. C. F.	36th wk., mild after meals	15 mg. p.r.n.	Partial relief
17. A. W. F.	21st wk., mild	15 mg. p.r.n.	Complete
18. S. B.	28th wk., severe at 1-2 A.M.	15 mg. p.r.n.	Complete
19. R. H.	16th wk., after meals	15 mg. (one dose)	Immediate and complete relief. Reaction—abdominal pain, headache
20. R. F.	20th wk., mild after meals	15 mg. (4 doses)	No relief

Discussion

Many of our cases complained of heartburn only at night, being awakened by the discomfort at two or three o'clock in the morning. Most of these found by experience that they obtained more benefit by waiting until the onset of the symptoms than by taking a prophylactic dose of the drug immediately prior to retiring. This was not unexpected since it was realized that the action of a single 15 mg. tablet of prostigmine bromide persists no more than a few hours at most. Nevertheless, a few patients stated that such a prophylactic dose ensured a full night's sleep without discomfort. Undoubtedly the diminished gastric motility with the consequent delay in absorption of the drug from the gastric and upper intestinal mucosae was one explanatory factor in these cases.

Inasmuch as the single, effective dose is so small, there is little or no likelihood of the appearance of any side reactions. Furthermore, there is no danger of the drug causing an interruption of the pregnancy, as has been shown on numerous occasions.¹¹⁻¹⁴

Summary

1. Heartburn of pregnancy is a very common condition.
2. It is now believed that a neuromuscular dysfunction of the esophagus and stomach is the underlying etiologic mechanism.

3. Prostigmine bromide by mouth is a rational therapeutic agent and has been demonstrated to afford prompt and complete relief in 15 out of 20 patients, and partial relief in another two.

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UNION CENTRAL BUILDING

THE ROUTINE USE OF STILBESTROL FOR ENGORGEMENT AND LACTATION IN NONNURSING MOTHERS

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THE employment of stilbestrol for the inhibition, suppression, prevention, or termination of engorgement and lactation has become rather popular. Some observers¹⁻⁵ have noted the prevention of engorgement of the breast and its associated pain with the use of stilbestrol. Others^{1, 6-9} have reported the inhibition, suppression, or prevention of lactation following its use. It is to be noted, however, that others^{10, 11} refer to the return of engorgement following the discontinuance of this hormone.

The foregoing prompted this study in an effort to determine the value of the routine use of stilbestrol in the prevention of engorgement, with its attendant pain, and lactation in nonnursing mothers.

This study is based upon the observation of 100 postpartum patients who did not nurse their babies for the following reasons:

1. Stillborn babies or babies that died shortly after birth.
2. Inverted nipples.
3. Difficulty with nursing following previous pregnancies.
4. Contemplated early return to employment.
5. Other children to be cared for at home.
6. Considering travel to be with husband who was in military service.
7. By preference, without any other reason.

These 100 patients were divided into two groups of 50 each, one of which received stilbestrol (diethylstilbestrol), and the other, a control group, who were not given any stilbestrol. In the former group stilbestrol was started within twenty-four hours of delivery. The dosage used was 10 mg., three times a day, for two days, followed by 5 mg., three times a day until the patient was discharged from the hospital. The oral route of administration was chosen.

The observations were recorded by the Obstetrical Nursing Supervisor, or, in her absence, by a nurse who was instructed by her, or by the attending physician. The observations included the noting of pain, engorgement, milk, fever, and erythema of the breast. The presence and degree of engorgement were determined by noting whether the breasts were soft, filling, full, or hard. If pain was present, the necessity for, and type of, relief required for the pain was recorded. Colostrum and milk were recorded as absent, expressed, or leaking.

None of the patients studied received any saline cathartics to prevent engorgement, and no restrictions were placed on fluid intake. Binders were used only when engorgement was present.

The period of study extended from Dec. 12, 1944, to Mar. 27, 1945. There were 93 private and 7 service patients in the entire series. The private cases represented patients of a number of physicians on the general staff as well as from the Department.

The type of delivery in the control group included: spontaneous, 34; low forceps, 6; mid-forceps, 2; version and breech extraction, 2; breech extraction, 1; bagging, version, and breech extraction, 1; and cesarean section, 6. There were two sets of twins in the foregoing group.

The type of delivery in those receiving stilbestrol included: spontaneous, 38; low forceps, 12; and breech extraction, 1. In this group there was one set of twins.

There were 24 primiparas, or 48 per cent, and 26 multiparas, or 52 per cent, in the control group. The corresponding figures for the stilbestrol group were: 21 primiparas, or 42 per cent; and 29 multiparas, or 58 per cent.

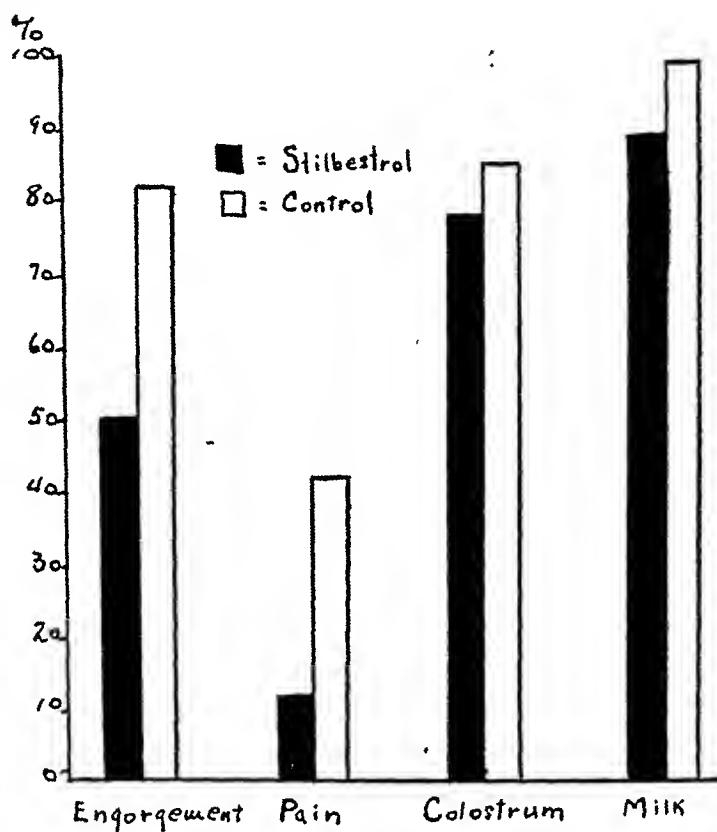


Fig. 1.—Comparative effects of stilbestrol upon engorgement, pain, colostrum, and milk in treated and control groups. Each column represents the percentage of patients in whom engorgement, pain, colostrum, and milk were present in the respective groups.

Results in the Stilbestrol Group

Engorgement was present in 25 patients, or 50 per cent, and absent in a similar number. The degree of engorgement was: filling in 10, or 20 per cent; full in 11, or 22 per cent; and hard in 4, or 8 per cent (Fig. 2).

Pain was present in 6 patients, or 12 per cent, and absent in 44, or 88 per cent. Relief of pain was not required in any patient in this group.

Colostrum could be expressed from the breasts in 39 patients, or 78 per cent, and was not present in 11, or 22 per cent. Leakage of colostrum was uniformly absent in this group.

Milk could be expressed, where there was no leakage of milk, in 28 patients, or 56 per cent. Leakage was present in 17, or 34 per cent of the patients, and absent in 5, or 10 per cent. Therefore, lactation was present in 90 per cent of this group, as manifested by leakage or expression of milk.

Fever was present in one patient, but could not be attributed to the breasts, and was probably due to endometritis.

Erythema was not noted in any patient in this group.

It is of interest that 50 per cent of this group of patients developed full, painful breasts at some time within two weeks after leaving the hospital.

Results in the Control Group

Engorgement was present in 41 patients, or 82 per cent, and absent in 9, or 18 per cent, of this group. The degree of engorgement was filling in 2, or 4 per cent; full in 17, or 34 per cent; and hard in 22, or 44 per cent (Fig. 2).

There was pain of varying degree in 21, or 42 per cent, of patients in this group; and in 29, or 58 per cent, it was absent. Pain was severe enough to require relief in 6 patients, or 25 per cent of those having pain, or 12 per cent of the entire control group. For the relief of pain codeine and aspirin were used in 3 cases; codeine, aspirin, and ice cap in 2 cases; and codeine, aspirin, and breast pumping in 1 case (Table I).

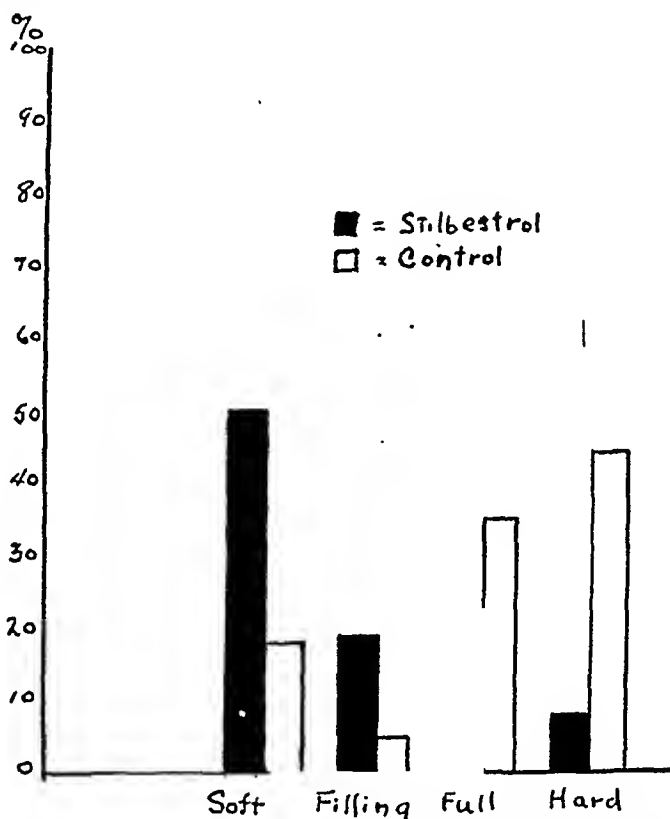


Fig. 2.—Relative degrees of engorgement in treated and control groups. Each column represents the percentage of patients in whom the various degrees of engorgement were present in the respective groups.

Colostrum could be expressed from the breasts in 42 patients, or 84 per cent, and was not present in 8, or 16 per cent. Leakage of colostrum was absent in all patients in this group.

Milk could be expressed, where leakage was not present, from the breasts of 12 patients, or 24 per cent. Leakage of milk was present in 38 patients, or 76 per cent. In other words, 50 patients, or 100 per cent of this group lactated, as manifested by leakage or expression of milk (Table II).

Fever was present in 5 patients, or 10 per cent of this group. In none, however, could the elevation of temperature be attributed to the breasts. It was apparently due to endometritis in 2, postcesarean pneumonia in 1, postcesarean infected abdominal wound in 1, and postcesarean (extraperitoneal) infection in 1.

Erythema of the breasts was not noted in any patient in this group.

The comparative effects of stilbestrol upon engorgement, pain, colostrum, and milk in the treated and control groups are shown in Fig. 1.

TABLE I. EFFECT OF STILBESTROL UPON PAIN

CONTROL GROUP				STILBESTROL GROUP			
PRESENT		ABSENT		PRESENT		ABSENT	
NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
21	42	29	58	6	12	44	88
Relief of pain was required for 6 patients, or 12 per cent of this group				Relief of pain was not required for any patient in this group			

TABLE II. EFFECT OF STILBESTROL UPON MILK SECRETION

CONTROL GROUP				STILBESTROL GROUP			
EXPRESSED		LEAKAGE		EXPRESSED		LEAKAGE	
NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
12	24	38	76	28	56	17	34
Lactation was present in 100 per cent of this group				Lactation was present in 90 per cent of this group			

Discussion

The observations in this study clearly indicate that the oral administration of stilbestrol to nonnursing patients by the method and in the amounts used prevents engorgement and inhibits lactation. It must be emphasized, however, that this action occurs only during the time of administration of the stilbestrol. Since it has been noted that engorgement appears in the period subsequent to the discontinuation of the hormone, one gathers the impression that engorgement is not actually prevented, but merely postponed, when this form of therapy is employed. In addition, engorgement of the breast is not always accompanied by pain. However, in this study where pain was present, it was always associated with engorgement. Furthermore, although pain was predominantly prevented by the use of stilbestrol, one must consider the degree of pain that was present in those patients not receiving the medication. From the experience gleaned from this study, showing that few patients require relief of pain with engorgement, we cannot help but feel that pain is practically a negligible symptom.

The inevitable conclusion from these observations is that stilbestrol exerts a definite physiologic action on the breast of the nonnursing patient in the method and amount employed. However, there is a question of the actual need for preventive therapy of this type, as determined by the minor degree of pain observed in this study. Furthermore, at this particular time, with the shortage of nursing personnel, the question might well be raised as to whether we are justified in burdening our nursing staffs with the added duty of supplying medication to patients, 88 per cent of whom do not require it. The remaining 12 per cent who might require relief of symptoms, if no prophylactic stilbestrol is used, can easily and effectively be treated by other medication should the occasion arise. In addition, stilbestrol used in this manner increases the cost of hospitalization, even though such expense is minimal, and the possible benefits to be derived from its use are negligible. Finally, in many instances the patient ultimately suffers from symptoms of delayed engorgement at an inopportune

time, i.e., at home, when she might have experienced the unpleasant symptoms in the hospital where they could be cared for under more favorable circumstances.

Notwithstanding the foregoing opinion, stilbestrol prophylactically has a definite place in the prevention of engorgement and suppression of lactation. It can be used with potential maximum benefit in postpartum patients in whom a slight degree of pain or the mechanical strain of engorged breasts may jeopardize recovery. Such conditions include cardiac decompensation, pneumonia, and other postpartum complications.

In the final analysis, one feels that this and previous studies demonstrate the physiologic action of an endocrine agent in an appropriate situation. From a practical therapeutic standpoint, however, the question may well be raised as to whether its routine use is really indicated.

Conclusions

1. The oral administration of stilbestrol in nonnursing mothers appears to prevent engorgement of the breast with its attendant pain. Actually, however, in many instances this is merely postponed.

2. Lactation is inhibited to a slight degree.

3. The advisability of routinely administering stilbestrol to nonnursing mothers for the prevention of painful, engorged, and lactating breasts is questionable.

The author wishes to acknowledge his appreciation of the assistance rendered in this study by Miss Gudrun Lund, Obstetrical Nursing Supervisor, and Miss Margaret A. Fay, Record Librarian of the Swedish Hospital.

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PENICILLIN IN OBSTETRICS*

A Preliminary Survey

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THE treatment of those obstetric complications in which infection creates the major hazard has long been a source of anxiety. The advent of sulfonamide therapy placed a potent weapon in our hands, one which we have no desire to minimize; however, experience with these preparations has shown a variety of side reactions which have limited therapy somewhat, and which must always be considered before the drug is used.

Among these contraindications and limitations are: nephritis, hepatitis, severe anemia, agranulocytosis, sensitization, nausea, urinary crystallization, and slow absorption from the gastrointestinal tract when its motility is impaired in the course of an acute infection.

Penicillin apparently produces no untoward reactions¹ and has reputedly a proved efficiency one thousand times greater than the sulfonamides.² The drug is usually administered parenterally and therefore there should be complete absorption of any given amount. The dosage used in this series was entirely empiric and could perhaps be safely reduced by resorting to any one of the various methods for prolonging the rate of absorption, namely: excretory blockade,³ suspension in oil and beeswax,⁴ local refrigeration,⁵ and suspension in plasma.⁶

The specific efficiency of penicillin has been proved by many investigators.¹ In obstetrics the *Streptococcus hemolyticus* is by far the most common invader and fortunately is extremely penicillin sensitive. There are a few strains of this and the staphylococci group which are penicillin resistant and therefore occasional failures may occur. In these cases, penicillin sensitivity may be readily assayed.⁷

Acute Mastitis.—Nine cases of acute mastitis are reported. The diagnostic criteria included pyrexia of 100° to 104° F., cellulitis, erythema, and localized tenderness. Two patients also exhibited initial chills and most of the patients appeared toxic. The onset of infection occurred between five and sixteen days post partum. One patient developed her symptoms fifty-two days post partum and was readmitted to the hospital for treatment.

The minimum dosage in this series was 180,000 units, the maximum 900,000 units, and was in direct proportion to the apparent virulence of the organism and the degree of breast involvement. Therapy was continued twenty-four to seventy-two hours. The patients were clinically cured within five days even though in all but one instance therapy was discontinued after forty-eight hours.

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†For lack of space, the extended tabulations of cases cannot be included here.

The erythema and cellulitis were invariably diminished 50 per cent within the first twenty-four hours of therapy and had practically disappeared in forty-eight hours. The patients were considered cured when temperature and pulse had been normal for three days and when there was complete absence of erythema, tenderness, and induration. In this latter respect the end results were much more satisfactory than those following sulfonamide therapy. Two patients resumed nursing, and it is probable that more could have done so on the basis of the rapidity and completeness of their recovery. No local therapy was used in this series.

Cesarean Section.—Penicillin was used sixteen times following cesarean section. In the first six patients administration was started immediately following operation. Under modern concepts of obstetrics, these patients were potentially or actually infected.⁹ Two had been in labor forty-six and forty-eight hours; one, fourteen hours; one, thirteen hours; one, twenty-four hours; and one, ninety-six hours. The membranes had been ruptured for eight, fourteen, thirty, forty-eight, and seventy-two hours. One of these patients had previously been subjected to radical cauterization of the cervix on two occasions, bilateral bartholineectomy with subsequent excision of fistulous tract and unilateral salpingo-oophorectomy; all for previous Neisserian infection. All the cesarean sections were of low cervical type except one, which was of the classical type. This latter patient had a fibroid uterus with extensive hysteroabdominal adhesions; the membranes had been ruptured for seventy-two hours and a Voorhees bag used unsuccessfully before admission. The patient had been in inertial labor for ninety-six hours, the cervix was dilated 3 cm., and the fetus had been dead at least forty-eight hours. The postoperative course of one patient in whom the membranes had been ruptured for thirty hours and who had been in inertial labor for twenty-four hours was absolutely afebrile. Three patients exhibited first febrile zone reactions, and two, second febrile zone.⁸ Temperature and pulse returned to normal in two patients in forty-eight hours, in one patient in seventy-two hours, in another in ninety-six hours, and in the patient upon whom classical section had been performed in one hundred twenty hours.

The minimum dosage of penicillin in this series was 100,000 units, the maximum dosage 900,000 units.

All patients left the hospital within fourteen days after operation.

Uterine cultures were taken on four patients at operation; three were negative and one positive for hemolytic streptococcus.

There was no maternal mortality.

In the other ten patients therapy was started when clinical evidence of infection appeared. Sections were as follows: three classical, four low cervical, two extraperitoneal supravaginal, and one Porro. In seven patients the membranes were intact; in three they had been ruptured seven, twenty-two, and forty hours, respectively. Three patients were not in labor; five were in labor eighteen, twenty, thirty-six, forty-four, and sixty hours, respectively. Two patients were sectioned for abruptio placentae. The postoperative febrile reaction in all instances reached the second zone. Of two uterine cultures taken at operation, one was positive for hemolytic streptococcus.

The minimum dosage of penicillin was 225,000 units; the maximum, 1,575,000. Five patients received supplementary sulfonamide therapy but in only three instances could the amount be considered of any therapeutic value.

The shortest hospital stay was sixteen days, the longest forty-two days. It is apparent that withholding penicillin therapy until the onset of clinical symptoms of infection definitely prolonged hospitalization and increased dosage.

There was no maternal mortality.

Endometritis.—Under the heading of endometritis we have grouped a series of eleven patients who had been delivered vaginally and who exhibited pyrexia, profuse foul lochia, uterine tenderness, and systemic toxicity. The uterine cultures contained hemolytic streptococci and *Staphylococcus albus*.

The complications of labor included two cases of retained placenta with postpartum hemorrhage, and two cases of inertial labor with transverse arrest. In seven patients no

apparent complications occurred during labor. In seven instances there were no operative procedures; in two the placenta was removed manually and the uterus was packed. One patient was delivered by internal podalic version and extraction; and, following an inertial labor of ninety hours, one patient was delivered by internal podalic version and extraction preceded by the use of a Voorhees bag.

The lowest temperature elevation in this series was 100°, the highest 108° F.

Sulfonamide therapy of inadequate dosage was given to two patients.

The minimum dosage of penicillin was 195,000 units; the maximum dosage was 1,375,000 units in a patient whose uterine culture was positive for *Staph. albus*.

The febrile reaction following penicillin therapy lasted twenty-four hours in three instances, forty-eight hours in three, seventy-two hours in two, ninety-six hours in one, one hundred forty-four hours in one, and one hundred sixty-eight hours in one.

The shortest hospital stay was nine days in a patient who had a pure culture of hemolytic streptococci and the longest hospital stay was twenty-two days in the patient who had *Staph. albus* culture.

There was no maternal mortality.

Septic Abortion.—There were four cases of septic abortion and one incomplete induced abortion, in whom, despite a normal temperature, *Staph. albus* was cultured from the uterus. Three of these patients had moderate to severe secondary anemia. One patient had 710,000 red blood cells and a hemoglobin of 16 per cent; the other two patients had hemoglobins of 40 and 65 per cent, respectively. Hemolytic streptococcus and *Staph. albus* were positive findings in four of the five patients.

One patient received four transfusions; one, three transfusions; and one, two transfusions. Two had secondary evacuation of retained placental tissue. One had an afebrile course, two had pyrexia for three days, one for six days, and one for thirteen days. Inadequate sulfonamide therapy was used in one patient. The dosage of penicillin administered ranged from 320,000 to 1,200,000 units. Temperature and pulse remained normal in one patient, and fell to normal in twenty-four hours, seventy-two hours, ninety-six hours, and one hundred forty-four hours, respectively, in the remaining patients.

The shortest hospital stay was eleven days; the longest was nineteen days. All recoveries were complete.

Gonorrheal Infection.—There were three cases of proved gonorrheal infection. One prenatal patient had an acute unilateral Bartholinitis which was draining on admission. Smear from the infected area was negative in forty-eight hours following administration of 200,000 units of penicillin. One patient had a positive smear following incomplete septic abortion and was discharged as cured ten days after admission following administration of 665,000 units of penicillin.

One baby developed ophthalmia neonatorum. Cultures were negative in twenty-four hours following local and systemic treatment.

Pyelitis.—One patient developed pyelitis. Urine culture was positive for streptococcus. She was given penicillin with definite improvement in her symptomatology. In this case other complicating factors prolonged her convalescence.

Pelvic Cellulitis.—One patient with history of retained placenta in both previous deliveries again required manual removal. Following an average hospital tenure she was readmitted ten days later with massive pelvic cellulitis and showed no improvement in spite of apparently adequate penicillin therapy. It is possible that the organism in this instance may have been penicillin resistant.

Phlebitis.—Penicillin was given to two patients for phlebitis. In one of these patients the temperature dropped to normal following 200,000 units. A sympathetic block, however, preceded this therapy. The other patient showed no improvement. She had received 240,000 units of penicillin.

Acute Suppurative Mastitis.—One patient was admitted with acute suppurative mastitis. This was treated with sulfonamides, hot compresses, and incision and drainage. Erythema, induration, and tenderness persisted, and new areas apparently were developing.

Three hundred thousand units of penicillin were given. The breast was considered free of infection within forty-eight hours and convalescence was uneventful.

Summary

We have reported a series of forty-five patients treated with penicillin. Penicillin was given to nine patients for early acute mastitis.

Penicillin was used prophylactically in six patients subjected to cesarean section following complicated labors. Each of these patients could well have had a stormy convalescence. The drug was given to ten other patients following cesarean section when clinical evidence of infection was present.

Eleven patients with postpartum infection were treated.

Five septic abortions are included in this report.

Three cases of known gonorrheal infection, one of pyelitis, one of pelvic cellulitis, two of thrombophlebitis, and one of acute suppurative mastitis are also included.

Conclusions

1. Penicillin apparently deserves serious consideration in obstetric complications attended by infection, potential or actual.

2. Acute mastitis responds with amazing rapidity. It is possible that lactation may be resumed.

3. The prophylactic administration of penicillin following prolonged rupture of membranes, prolonged inertial labors, and in other patients potentially infected is apparently effective in assuring a smooth convalescence and in shortening the period of hospitalization. If this is substantiated by further investigation, it will undoubtedly broaden the use of low cervical cesarean section. A routine culture should probably be taken from the lower uterine segment at operation.

4. The treatment of infection following cesarean section in this series has been effective.

5. In incomplete septic abortion, particularly where there is a marked secondary anemia, a leucopenia, or both, penicillin is undoubtedly safer than the sulfonamides. The absence of other undesirable features of sulfonamide therapy will also recommend this drug.

6. Previously reported efficacy in the treatment of gonorrheal infection is substantiated.

7. Pyelitis due to streptococcal infection may indicate penicillin therapy.

8. Our sole experience with postpartum pelvic cellulitis was disappointing; however, an occasional penicillin-resistant streptococcus or staphylococcus will undoubtedly be encountered, and may have been a factor.

9. No conclusions can be drawn concerning phlebitis.

10. Penicillin is apparently of value in the postoperative treatment of acute suppurative mastitis and may eliminate additional surgery. The disappearance of any vestige of induration has been an outstanding finding in our mastitis results.

11. This small series, in which there were no mortalities and in which the hospital stay was of shorter duration than one would expect, warrants accumulation of additional data.

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4709 FIFTH AVENUE

PRESACRAL SYMPATHECTOMY FOR INTRACTABLE FUNCTIONAL UTERINE PAIN*

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IN DISCUSSING even briefly any form of medical or surgical therapy for functional pelvic pain, which in most instances means uterine pain, an exposition of the supposed etiology of the condition is obligatory, for the treatment of this distressing disturbance is not solved by the exhibition of a few drugs, the manipulation of organs, nor necessarily the eradication of certain pain tracts.

In this connection, a casual acquaintance with ethnographic history through uncounted ages is illuminating, for it depicts the psychic blight under which menstruating women lived in primitive and medieval society. Now we are somewhat better informed on the physiology and pathology of menstruation. But without proper and due consideration of its psychological aspects, it is impossible to understand completely this fundamental evidence of femininity.

Of the various disturbances associated with menstruation, dysmenorrhea is patently the most common and most important of the functional alterations. The investigation of the cause of dysmenorrhea clearly involves as a first procedure a most thorough gynecologic examination. This will serve to determine whether or not the pain is really functional. All too often, however, will minor disturbances in the pelvis be found which by no stretch of the imagination, other than that of an eager surgeon, could possibly serve as a cause for the expressed pain. Nor do some of the occasional good results from surgical management of uterine malposition, asymptomatic ovarian cysts, cervical erosions, etc., justify the assumption that they were curative specifically for the pain of which the patient had been relieved. In many instances, they are merely the psychological placebos which relieve the psychogenic pain and often are only as long lasting as a placebo may be.

Let one but review the operating schedules on the gynecologic wards of twenty years ago with those of today and note how time and experience have dealt with displacements of the uterus as causes for female pelvic pain, or whatever else the patient complained of. The same applies to cervical stenosis. Congenital failure of development or infantile uterus, follicular cysts of the ovary, and a variety of other conditions, are given as causes for dysmenorrhea. At present, endocrine deficiencies of one type or another, or all types put together, are assumed as etiological factors. If the physician is sufficiently observant, experienced, and honest, and has sustained enough disappointments in therapy, he inevitably recognizes the psychoneurotic side of dysmenorrhea. The more he knows of conditioning factors and psychological trauma of the patient's early girlhood and adolescence, the more will he consider her psychological

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rather than her gynecologic poise. A woman with any psychoneurotic tendency or imbalance may make the all-important and ultrafeminine mechanism of menstruation the subconscious recipient of emotional fears and terrors to produce the symptom of dysmenorrhea.

The failure to find any basic pathologic or anatomic change in the uterus with any degree of consistency in the vast majority of these girls, the modification of the pain in any given period by unexpected happenings, the relief experienced by impossible medication, spontaneous relief through sexual activity or pregnancy, all show the tendency of the symptom complex to be as unpredictable and as unsolvable as the symptom complex of "nervous indigestion."

From the foregoing it is manifest that I do not regard functional uterine pain, or dysmenorrhea associated with minor degree of pelvic pathology, which experience has shown not definitely pain producing, entities necessarily responsive to medical, surgical, or endocrine therapy. Rather is it commonly a psychosomatic unit, the understanding of which on a psychological basis is more important than the understanding of the patient's pelvis. It is with some temerity, therefore, that I propose to discuss and give the results of a surgical therapeutic approach to this problem for sharply defined group of patients. The operation of *presacral sympathectomy* in itself is symptomatic therapy, since the pain-producing agent is not the presacral plexus. It is merely the tract by which the painful impulses are transmitted. Until our understanding of psychological and pathologic processes improve, however, we will continue to apply nonspecific surgical treatment in order to gain symptomatic relief. The application of this statement is to be found in our present surgical approach to the problem of hyperthyroidism, where few of us believe that the thyroid gland itself is the primary offender. It is the responsive or reacting agent to outer disturbances, and it is the violence of the reaction which we seek to control by surgery, rather than eradication of the initiating disorder. My attitude toward the utilization of presacral sympathectomy for dysmenorrhea is comparable to that just expressed. I regard it as a means of severing the paths of painful uterine stimuli, no matter how produced, and in spite of the admitted probability that it is often a painful psychosomatic disorder of psychogenic origin. Nor do I expect that the operation will prevent necessarily the transference of an emotional conflict to another organ or organ-group with the development of symptoms, the character of which are dependent upon the organ neurosis engendered. Certain alterations of menstruation may be explained by the action of the central regulating mechanism in the brain and medulla oblongata exerting control on the autonomic regulating mechanism of the hypogastric (genital) plexus. (Parenthetically, the association of control may be better understood by recalling that to be found between the olfactory and genital organs of the dog.) Obviously, however, such alterations cannot be painful if the pain-carrying visceral afferent fibers are divided. However, it will, in carefully selected cases, eventuate in a cessation of uterine pain and an eradication of pain fixation to a fundamental and recurrent physiologic process. It is conceivable that transfer of symptoms might be to a more easily controlled sphere, or one less periodic or anticipated in form.

The innervation of the uterus is both by the sympathetic and parasympathetic systems. The motor fibers arise above the sixth and probably in the fourth dorsal segments of the cord, reaching the sympathetic chain by way of the white rami communicantes and traveling thence by the sympathetic plexuses to reach the uterus. Section of the cord at that level by injury or by high spinal or caudal anesthesia abolishes uterine contraction. This fact has been demonstrated and employed clinically to completely arrest premature labor contractions. Labor stops and the patient may be carried to term.



Fig. 1.—Cross section of approximately one-fourth of a resected plexus shows eight sympathetic fibers of major size. ($\times 75$.)

This autonomic mechanism is counteracted by the parasympathetic fibers of the sacral division, for when the influence of the latter is abolished by sacral anesthesia, there is cervical relaxation and an increase in tone and force of uterine contractions, but no alleviation of pain. Obviously, the sacral parasympathetics carry no uterine pain sensations, although the pain of dilatation of cervix and vagina is relieved. Anesthesia involving the eleventh and twelfth thoracic segments causes complete cessation of uterine pain without impairing uterine contractions. It is thereby demonstrated that the centripetal fibers transmitting painful uterine stimuli pass to this level. These sensory afferent fibers travel with the sympathetic nerves, and will be found in the superior hypogastric (presacral) plexus (Fig. 1).

It is evident therefore, that removal of the presacral plexus will arrest painful stimuli from the uterus, without materially altering those from cervix or upper vagina. The fibers carrying these pain sensations are regarded as special visceral afferents anatomically and functionally distinct from the sympathetics

with which they travel, since they are poorly myelinated, and course to the cord with no ganglion synapse before entering the posterior spinal root. All of our specimens of resected plexuses were submitted for examination (Dr. N. M. Alter) and a considerable number of ganglia were found. This is not in accord with the commonly held opinion that there are no ganglia in the presacral or superior hypogastric plexus. We regard these as ectopic ganglia of the sympathetic efferents, and not associated with the special visceral afferent pain tracts. (Figs 2 and 3.)

Since most of the motor sympathetics follow the aorta, hypogastric, and uterine arteries, to enter the uterus via the ganglion of Frankenhäuser, presacral sympathectomy will not obliterate the functional motor effectiveness of the sympathetic nerve supply. Theoretically, therefore, uterine pain relief without marked motor alteration may be expected. It is likewise apparent that the effectiveness of a presacral resection may be accurately presaged by inducing a sympathetic block at the eleventh and twelfth dorsal segments, where the special uterine afferents enter the dorsal roots with the sympathetic chain. *

The following cases are selected from a larger group. They are presented because they illustrate in their case histories innocuous associated pathology, constitutional inadequacy, symptom transfer, and previous useless operations and hormone therapy. The pain relief after presacral sympathectomy is unquestionably ascribable to thorough removal of the plexus in such cases.

CASE 1.—Patient single, aged 19 years.

Surgical history: Mastoid operation, 1931 and 1942. Appendectomy and removal of two ovarian cysts, 1942.

Chief complaint: Severe dysmenorrhea since onset of flow, extremely severe for past six months, and in no wise relieved by the operation done one and one-half years ago. Frequent brownish vaginal discharge between periods. Also enuresis for years.

Examination and operative findings: Nothing except an innocuous lime-sized cyst of the right paraöphoron.

Operation, March, 1944: Cyst was removed, uterosacral ligaments shortened with Pagenstecher suture. A presacral sympathectomy was then performed. The first menstruation occurred six weeks after operation with absolutely no pain. However, since this girl had enuresis for years at night, psychoanalysis was recommended, but this was not carried out. She has had no pain with her periods since the operation, but believes her enuresis is worse. This may well represent a symptom transfer.

CASE 2.—White, well-developed woman, 25 years old, married five years but separated. Nothing of importance in the past history.

Chief complaint: Severe dysmenorrhea for nine years, becoming progressively worse, necessitating the loss of three to five days from her work each month.

Previous treatment: Various types of douches, one dilatation and curettage, one cervical dilatation, repeated injections of various types of hormones, and all forms of empiric oral treatment before she was seen here.

Pelvic examination: No pathology.

Because of the marital derangement, psychotherapy was first instituted after she was seen in May, 1942, combined with hormonal treatment. There was no improvement in her condition in the next fifteen months. Periods were associated with severe pain, nausea, and vomiting, and she was desperate for relief.

On Aug. 17, 1943, under 100 mg. of spinal anesthesia, a presacral sympathectomy was carried out, accompanied by an incidental appendectomy. Both tubes were markedly thickened at the cornual end with typical isthmica nodosa present. These were not touched. Except for one spell of pain with a left sacroiliac strain and sciatica in June, 1944, the patient has been well and free of all menstrual pain since the operation.

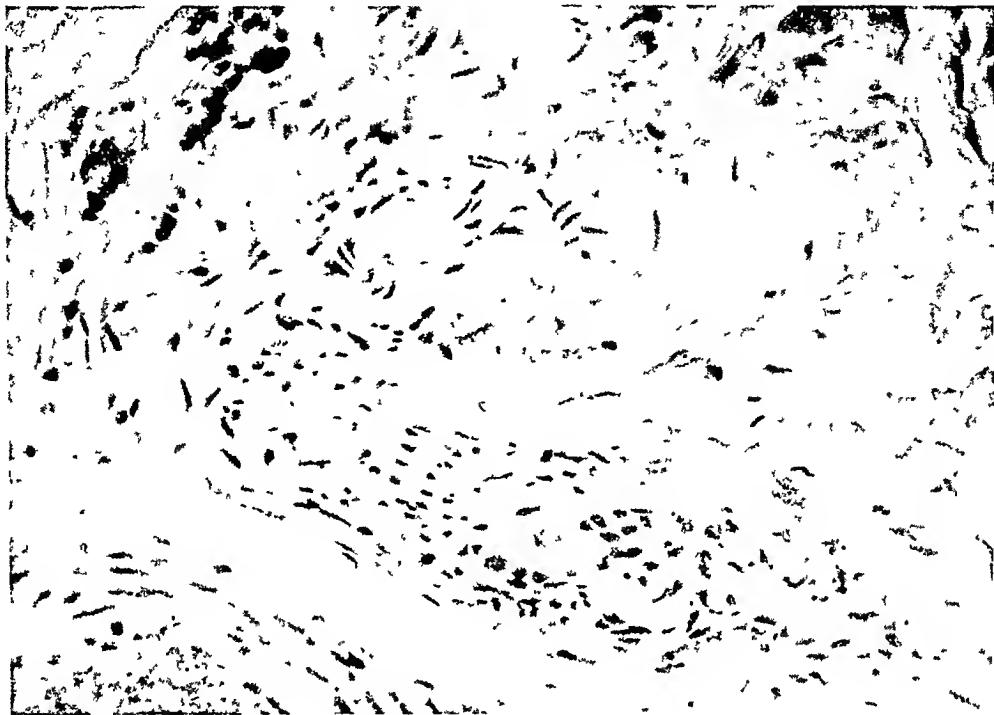


Fig. 2.—Presacral (hypogastric) sympathetic nerve fiber with distinct ganglion cells. ($\times 160$.)

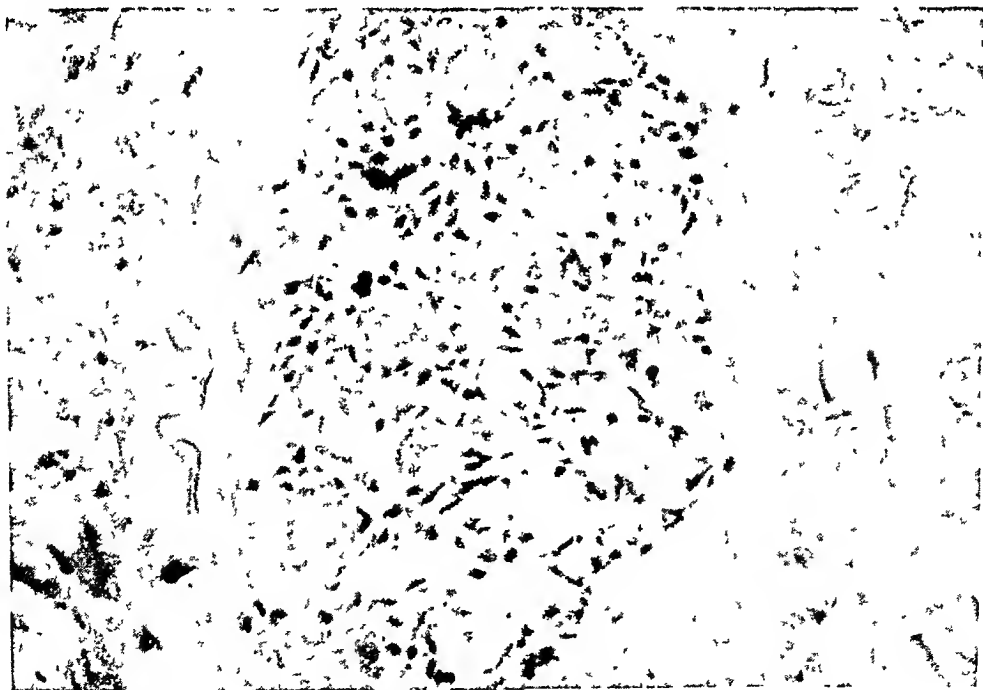


Fig. 3.—A complete ganglion showing numerous nerve cells, removed with the presacral (hypogastric) plexus. It is not commonly admitted that such ganglia exist in this area. ($\times 384$.)

CASE 3.—White, well-developed woman of 33 years, married six years. No pregnancies. Seen May, 1943. Previous surgical experiences, all for dysmenorrhea, were: operation, 1939, dilatation and curettage; 1942, dilatation and curettage; 1943, dilatation of cervix.

Chief complaint: Severe dysmenorrhea ever since patient started to menstruate at the age of 13 years, becoming worse the past two years, causing complete prostration for twenty-four to forty-eight hours after its onset. She experienced no relief following the surgical procedures mentioned above. No physical findings of interest, the uterus being small, anteflexed, and probably underdeveloped.

Treatment: She was treated with various medications and hormone therapy for three months without relief. In January, 1944, an operation was done in which there were no pathologic pelvic findings. A presacral sympathectomy was done with complete resection of all the nerve-bearing tissue in the interiliac trigone. An incidental appendectomy was also performed.

The patient began to menstruate four days after the operation, while in bed in the hospital, without being aware of the onset of her flow. She has been followed to date and her report is that she has been completely relieved of pain. Her only notation is that her periods seem somewhat more profuse than formerly.

Conclusions

Functional uterine pain commonly represents a psychosomatic disorder affixed to the predominant emblem of femininity. Psychotherapy offers more promise than correction of coexistent but completely innocuous findings of minor pelvic pathology.

When other treatment is inadequate, the pain may be effectively relieved by presacral sympathectomy. In patients with apparent emotional instability a preliminary low dorsal sympathetic block given at the onset of menstruation may be used as a diagnostic measure for pain-relief prognosis. Presacral sympathectomy will give the most notable results in cases with functional uterine pain similar to those quoted. It is also recommended as a surgical adjuvant where dysmenorrhea is an outstanding symptom-accompaniment to conditions such as impacted adherent retroversion and pelvic endometriosis with probable adenomyosis uteri in young women. It should be strictly limited in its application to patients who first have been competently treated by nonoperative methods, and should be performed by surgeons capable of removing the plexus in its entirety. The pain tracts in the special visceral afferent fibers must be completely severed to effect complete relief.

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INITIAL FETAL ATELECTASIS

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WHETHER the human fetal lung is atelectatic until birth is a question which has been debated for many years. Some have maintained that, due to intrauterine respiratory movements, the amniotic fluid enters the lung and may assist in dilating the alveoli in preparation for air breathing. Others, while admitting that intrauterine respiratory movements occur, view with apprehension the entry of amniotic fluid into the lung. It is pertinent to review the literature presenting the evidence.

As long ago as 1888, Ahlfeld¹ described rhythmic fetal movements which he observed in patients during the latter weeks of pregnancy. He suggested that this fetal activity was due to respiratory efforts and thought that aspiration of the amniotic fluid must occur. Many disagreed with this theory, but, in 1905, he again restated his beliefs, and produced convincing graphic records of the respiratory movements.² In the polemic which resulted, other investigators observed the intrauterine respiratory movements, but concluded that the force of the respiratory efforts was too weak to suck fluid beyond the usually closed fetal glottis.³ The argument then subsided, but has been raised again recently by investigators⁴ who demonstrated that respiratory movements draw amniotic fluid into the lungs. It was also stated: "There is evidence that intrauterine respiration is of a functional significance in the development of a normal lung, aiding in dilatation in alveoli and elastic walls of the future air passages."⁵

The injection of radiopaque material into the amniotic sac of experimental animals and the human being was attended by significant results. In the unanesthetized and unoperated guinea pig, the radiopaque material appeared in the lungs only when anoxemia was present.⁶ In the human experiments, the use of thorotrast seems to indicate that fetuses of six months' gestation do aspirate amniotic fluid in utero.⁷ Other similar experiments^{6, 8} were performed in the human being with results which may be questioned, since we do not know whether physiologically normal conditions prevailed.

The experimental injections of dyes^{4, 9, 10, 12} or particulate matter into the amniotic sac, and studies of the vernix-filled lungs from stillborn infants¹³ have proved that aspiration of amniotic sac contents can occur. The experimental evidence available at the present time seems to indicate that fetuses are apneic during the greater part of gestation, and that fetuses whose oxygen requirements are adequately met are apneic until birth.¹⁴

Differences in opinion would seem to depend upon lack of knowledge of the normal structure of the fetal lung at full term. This paper briefly presents two congenital anomalies which may clarify the structural picture of the lung just before birth.

Method

Two stillborn fetuses were used and prepared in the following manner. As soon as possible following delivery, the trachea was exposed, clamped, and tied by ligature slightly above the thyroid gland. The fetuses were fixed by vascular perfusion with formalin. After

*Presented before a meeting of the Clinic Gynecological Society, Jan. 19, 1945.

removing the skin, subcutaneous tissues, and large chest muscles, they were immersed in 10 per cent formalin until the lungs hardened in situ. The fetal lungs were then removed, blocks were cut from representative regions, and sections were made. These were stained by the routine hematoxylin and eosin method, and for epithelial elements by the Gram method decolorized by acid alcohol.

Case Reports

CASE 1.—S. B. (Hosp. No. 185541). The mother was a primipara, aged 25 years. Her last menstrual period was April 10, 1943. The term date was Jan. 17, 1944. The fetal heart tones disappeared or were not heard five hours before delivery. After the fetal heart tones were no longer heard, x-ray revealed the presence of a single anencephalic monster. The fetus was delivered spontaneously Nov. 27, 1943. The pathologic report was as follows: The body is that of an anencephalic female premature infant with a body length of 36 cm.; weight, 1,360 grams; and an estimated intrauterine age of seven lunar months. There is a complete absence of the cranial vault and, though the occiput is formed, there is a defect at the site of the anterior fontanel measuring 4 by 2 cm. through which protrudes some nervous tissue representing a rudimentary brain measuring 3 by 2 by 1 cm. The neck is not formed so that the head is between the shoulders.

CASE 2.—S. B. (Hosp. No. 185627). The mother was a multipara, aged 28 years. Her last menstrual period was March 22, 1943. The term date was Dec. 29, 1943. No fetal heart tones were heard at any time during labor. X-ray examination showed presence of a single anencephalic monster. The fetus was born Dec. 4, 1943. The pathologic report was as follows: The body is that of an anencephalic male premature infant with a body length of 41 cm., and an estimated intrauterine age of eight lunar months. The fetus weighs 1,650 grams. The head shows a complete absence of the cranial bones and a small amount of exposed nervous tissue represents a rudimentary brain in the malformed base of the skull.

Results

The lungs of these two fetuses showed complete atelectasis. They were compact gland-like organs whose respiratory passages were not filled. The larger bronchioles could be easily identified and had large lumina. The smaller bronchioles had folds of epithelium in them, whereas the more distal passages were either solid masses or partially formed alveoli. The epithelium of the alveoli was cuboidal or columnar, although all boundaries were not definite. Nuclei were spherical to ovoidal and stained darkly with hematoxylin. No epithelial elements were identified in the bronchioles or in the smaller passages. When present, cornified epithelial cells appear as long irregularly wavy coarse structures often turned on edge. Amniotic fluid, when present in the lungs, usually appears as a precipitate.

Discussion

Histologically, the lungs of the stillborn infant contain many fluid-filled alveoli and alveolar ducts.^{15, 16} Similarly, in experimental animals it has been observed that fluid-filled spaces occupy 20 to 30 per cent of the lungs before breathing has commenced.¹⁷ These observations suggest that fluid contained in the fetal lung is coextensive with that in the amniotic cavity. There is no proof that this is the normal condition because it is possible that, during the death of the fetus in utero, asphyxial conditions had induced intrauterine respiratory movements and led to aspiration.

Experimental evidence indicated that the lung of the guinea pig at full term is compact and hence the expanded fluid-filled lungs in question do not present a true picture of apneic fetuses.¹⁴ Reasoning from this and from correlated studies on anoxia, it seemed probable that an initial atelectasis is the

normal state in the lung of human fetuses. The two cases presented above may be regarded as an important link in the chain of evidence supporting this hypothesis. The fact that a marked anencephalus was present in each case suggests that there was a definite disturbance if not actual lack of central nervous system control of the body. Hence, it is highly probable that the fetuses in the final agonal movements preceding death were not able to make the dyspneic gasps observed in anoxic experimental animals. Therefore, the lungs were in the condition of a normal birth at term, namely, in the state of atelectasis. Thus, it was possible to secure in the human being a lung preparation very similar to that found in the experimental animal. Lungs of stillborn infants which have died asphyxial deaths in utero usually are partly expanded. Their bronchioles are opened, and the epithelial linings of ducts and alveoli are lower than in the atelectatic specimens. Masses of debris found in the amniotic fluid usually are present in the lumina of the bronchioles and alveolar ducts. In the cases presented the lungs were solid glandlike structures. There was no tracheal obstruction. The amniotic fluid had easy and complete access, and yet the alveoli were unexpanded and no microscopic evidence of the amniotic fluid or its contents was found. It has been concluded that intrauterine respiration in the experimental animal either does not occur or is too weak to cause aspiration of amniotic fluid. It is very possible that the same situation obtains in man. Indeed, Windle,¹⁴ after analyzing the observations of Potter and Bohlender,¹⁵ and others, makes the opposite suggestion, namely, that the lung contributes a gentle but persistent flow of transudate to the amniotic fluid.

We are not concerned with the histology of the pulmonary alveoli in this paper. If, however, it is appreciated that atelectasis persists until birth, then normally the cuboidal epithelium probably is present until air breathing is initiated and only then rapidly becomes thinner. This is demonstrated experimentally by Bensley and Groff,¹⁶ who observed that cuboidal epithelium persists as a lining of the pulmonary alveoli of the rat as late as the day before birth.

Summary

The existence of fetal atelectasis until birth has been well demonstrated in laboratory animals. A similar condition was thought to be present in the human fetal lung at term, but, because of the obvious difficulties in securing a specimen, this was never proved. The writer was fortunate in having fetuses which, because of an embryologic defect of the central nervous system, closely simulated the condition under which the lungs in experimental animals are studied. Since the results are similar, it is suggested that the initial atelectasis of the fetal lung persists in man until birth.

The author is greatly indebted to Dr. John McCarter for his assistance in the preparation of the specimens.

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Discussion

DR. WILLIAM F. WINDLE.—I have seen these microscopic preparations and believe they are in line with observations on experimental animals from my own laboratory. My colleagues and I have published several articles dealing with experiments demonstrating a state of initial atelectasis in the full-term guinea pig. When we published our observations, we did not think that anyone would ever demonstrate comparable pictures of the unexpanded fetal lung in the human being. I have seen small areas of initial atelectasis in stillborn human lungs, such as were described by Dr. Sidney Farber some years ago, but always there were many alveoli filled with aspirated material from the amniotic sac.

The lungs of almost any animal which has reached a state of maturity comparable to that of Dr. Zettelman's anencephalic human fetuses would be found in a state of partial expansion with amniotic fluid if death and the accompanying fetal asphyxiation should intervene before birth. This was not the case in Dr. Zettelman's anencephalic specimens and the reason may be that his specimens lacked a sufficiently well-organized respiratory center to respond to the stimulus of asphyxia.

I believe that the studies of Dr. Zettelman serve to complete the picture of conditions during fetal life. We now have a much better understanding of fetal respiration than we had a few years ago.

DR. EDITH L. POTTER.—The experimental approach has not yielded unequivocal results, and whether one accepts the tenet that, in the rabbit, guinea pig, and sheep, intrauterine respiration with an accompanying inflow of amniotic fluid is normal, or whether one believes this phenomenon never occurs except when the respiratory center is stimulated by a reduction in oxygen, appears to be largely determined by one's personal acquaintance with a particular group of investigators.

The problem in the human fetus is still more difficult of direct solution, and it is necessary to rely largely on indirect evidence. The material which has just been presented is a careful study prepared in an attempt to picture the normal intrauterine appearance of the human fetal lung and to show, thereby, that the pattern usually described as normal is not normal and is the result of anoxia with secondary aspiration of fluid.

Extreme caution must be exercised in the choice of material which is to be used to prove a point. The essayist has chosen the lungs from two extremely malformed fetuses weighing only 1,360 and 1,650 grams and has concluded that the appearance they present is what would be expected in a normal fetus at term, the average weight at this time being in excess of 3,400 grams.

My interest in the subject of intrauterine respiration has led me, in the last ten years, to examine histologic preparations of the lungs of over 5,000 human fetuses and newborn infants in all stages of development and exhibiting all types of pathologic lesions. Included

were the lungs of 106 anencephalic monsters, and the pattern just described gives an excellent picture of conditions as they frequently exist in the lungs of immature fetuses with this anomaly.

When any condition causes a reduction in the space available for lung growth, a definite inhibition of pulmonary maturation follows. Pleural effusions, massive cardiac hypertrophy, and diaphragmatic hernias, as well as the shortening of the thoracic cage which almost always accompanies anencephalus, not only cause a limitation in the size of the lungs, but in the degree of alveolar development. In fact, this has been cited by other investigators as proof that exchange of amniotic fluid is necessary for normal development, and the disproportionate immaturity is ascribed to forced inactivity of the lungs.

In my series of anencephalic monsters, the lungs from 47 show an average size only half to two-thirds that of normal infants of the same weight. Since the brain and calvarium are absent, the discrepancy is even greater than is indicated, for the body must be proportionately more mature in order to attain an equivalent weight.

In addition to the fact that the fetal anomaly may in itself be expected to alter the appearance of the lung, there is the further difference due to immaturity per se. Most organs at seven months' gestation, which is the age given by the essayist for one of his specimens, are very different from those at term. At this stage the liver shows marked erythropoiesis, the kidney has a wide nephrogenic zone and is actively producing glomeruli, and in the lung alveolar growth is in its early stages. The pattern in the lung as in the other organs, shows many changes between seven lunar months and ten lunar months.

There is insufficient time to describe the normal development of the lung, but suffice it to say that, in a fetus free of any visceral or skeletal anomaly, the lungs show constantly increasing differentiation and elaboration up to the time of birth, that as the pulmonary tree becomes more complex a lumen is normally present in all portions and opposing walls are not in contact, and that at thirty-eight weeks' gestation the alveoli are never lined by a continuous layer of cuboidal epithelium.

There is as yet no conclusive proof that the fluid normally present within the lungs is aspirated from the amniotic sac or is in any way related to pulmonary development. The fact that alveolar development has been shown to be normal, and that alveolar ducts and alveoli are not collapsed in portions of lungs which are completely devoid of communication with the pharynx indicates that the presence of amniotic fluid is not necessary for normal growth.

If, however, the absence of cuboidal epithelium lining the alveoli and the presence of lumens in the alveoli is evidence of asphyxiation, this discussant has never seen a nonasphyxiated stillborn fetus among almost three thousand whose lungs have been examined histologically.

DR. ZETTELMAN (Closing).—The weight of the brain and the missing calvarium in each of the cases which I reported would be about 400 grams, perhaps a little more. That, with the weight of the rest of the body in each case, would be well over 2,000 grams. I would like to say that we considered the lung of the anencephalic fetus not only normal, but, if it were in an infant that was average size, it would be considered practically normal.

NEOPLASMS IN APPARENTLY NORMAL OVARIES

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THE object of this paper is to emphasize the possible occurrence of neoplasms in apparently normal ovaries and to show that some of them can be detected at operation. We have examined the ovaries at all operations in which this was possible in the service of the Graduate Hospital, and in the past three years the following tumors were found in approximately 1,500 ovaries that appeared normal: three dermoids, one Brenner tumor, one fibroma, one papillary cyst adenocarcinoma, and one granulosa-cell tumor. Two of these tumors were discovered in the routine pathologic examination of ovaries removed at operation, five of them were found by examination of the ovary during the operation. These small neoplasms ranged in size from a few millimeters to 1.5 centimeters; none of the ovaries that harbored them were of more than normal size. This comprises a group of tumors of extreme interest in themselves, but a more important consideration lies in the practical aspect of the problem presented by their presence in apparently normal ovaries. Though they were mere infant growths when discovered, such tumors eventually would have enlarged, but their early discovery and removal averted serious consequences.

Microphotographs of the tumors and brief histories are herewith presented.

Case Reports

CASE 1.—Dermoid cyst. (Fig. 1.) Mrs. E. K. J., aged 37 years, was admitted to the hospital because of pain in the lower abdomen for the past two years. Preoperative diagnosis was ovarian cyst. A hysterectomy and bilateral salpingo-oophorectomy was done. One ovary contained a dermoid 9 cm. in diameter. The apparently normal ovary measured 4 by 3 by 2 cm.; it contained a dermoid 1.5 cm. in diameter.

CASE 2.—Dermoid cyst. (Fig. 2.) Mrs. A. B., aged 30 years, was admitted because of low abdominal pain and dysmenorrhea. Preoperative diagnosis was dermoid cyst. Partial left oophorectomy and right oophorectomy was done. She had a dermoid cyst of the right ovary which measured 10 by 7 by 5 cm. The apparently normal ovary measured 3.5 by 2 by 1.5 cm. grossly, while the dermoid in it was only 0.5 cm. in diameter. This cyst was resected, thus leaving a good ovary on the left side.

CASE 3.—Dermoid cyst. (Fig. 3.) Mrs. S. L., aged 62 years, was admitted because of menometrorrhagia for three years. Preoperative diagnosis was multinodular fibroid uterus. Hysterectomy and bilateral removal of tubes and ovaries was done. She had a large Brenner tumor of one ovary measuring 16.5 by 14 by 10 cm. The apparently normal ovary measured 2.3 by 1.6 by 1.3 cm., and contained a dermoid that measured 0.5 by 1.2 cm.

This small ovary offered no problem because of the patient's age, 62 years, but in a younger woman it might have been allowed to remain unless carefully examined on the table, since it could have been easily mistaken for a small hypoplastic ovary.

CASE 4.—Brenner tumor. (Fig. 4.) Mrs. E. H., aged 35 years, was admitted and operated upon because a mass (fibroid) was found in a routine examination which gave no symptoms. Preoperative diagnosis was fibroid of the uterus. Hysterectomy and salpingo-



a.



b.

Fig. 1.—a, A' = low power of a dermoid 1.5 cm. in diameter in an ovary measuring 4 by 3 by 2 cm. b, High power of a portion of the dermoid showing squamous epithelium, sebaceous glands and a hair follicle.

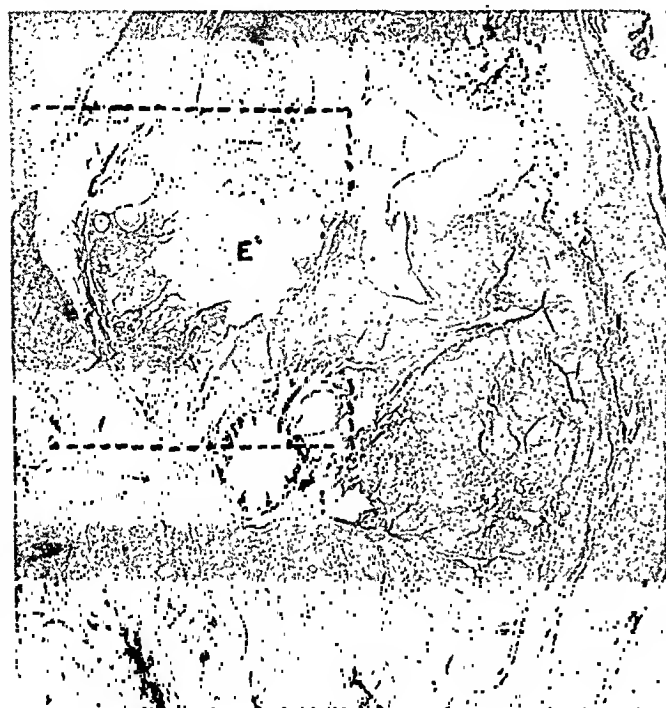


a.



b.

Fig. 2.—a, C' = low power of a dermoid 0.5 cm. in diameter in an ovary measuring 3.5 by 2 by 1.5 cm. b, High power of the dermoid showing sebaceous glands and squamous epithelium.



a.



b.

Fig. 3.—*a*, *E'* = low power of a dermoid measuring 0.5 by 1.2 cm. in an ovary measuring 2.3 by 1.6 by 1.3 cm. *b*, High power of the dermoid showing squamous epithelium and sebaceous glands. It also contained hair follicles, sweat glands, columnar epithelium of intestinal origin, and a nodule of bone.



a.

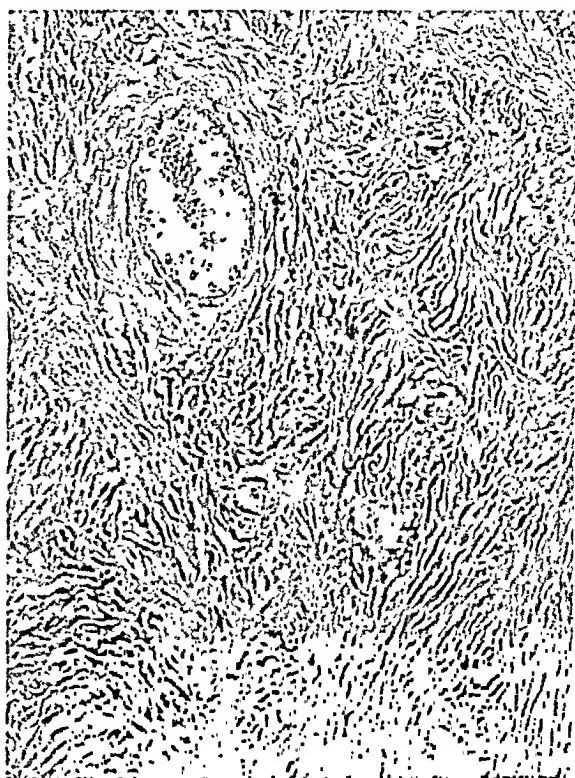


b.

Fig. 4.—*a*, *G'* = low power of a Brenner tumor measuring 1 by 0.75 cm. in an ovary measuring 4.5 by 3.5 by 2 cm. *b*, High power of the Brenner tumor showing one of the islands of epithelioid cells surrounded by connective tissue stroma.

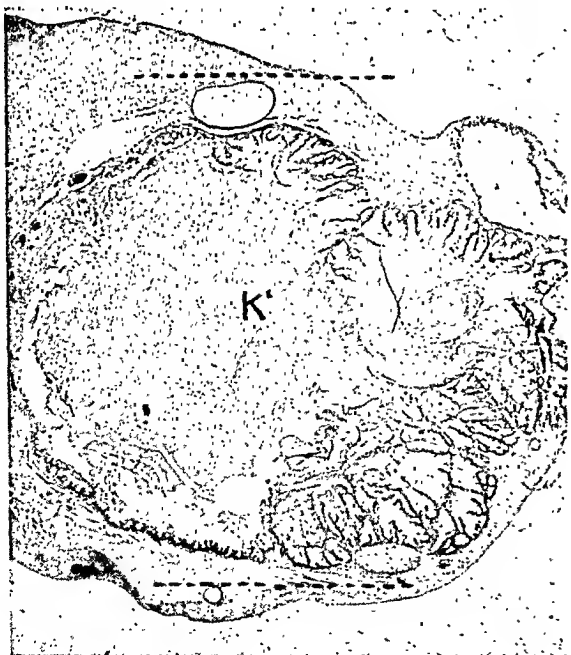


a.



b.

Fig. 5.—*a*, I' = low power of a fibroma measuring 1 by 1.5 by 1.7 cm. situated at the end of an ovary that measured 3.5 by 2.3 by 2 cm. (only small piece of ovary seen in micro-photo). *b*, High power of the fibroma.



a.



b.

Fig. 6.—*a*, K' = low power of a papillary cyst adenocarcinoma of the pseudomucinous type measuring 1.7 by 1.2 by 1.4 cm. in an ovary that measured 4 by 2.5 by 1.5 cm. *b*, High power of a portion of the malignant cyst.

oophorectomy was done. One tube and ovary had been removed at a previous operation. She had a fibroid of the uterus, and an ovary that measured 4.5 by 3.5 by 2 cm., with a Brenner tumor at one pole that measured 1 by 0.75 cm.

This ovary was removed because of its microcystic character and the nodule at one pole; resection would have left practically no ovary.

CASE 5.—Fibroma. (Fig. 5.) Mrs. M. D., aged 35 years, was admitted with the chief complaint of leucorrhea and low abdominal pain. Preoperative diagnosis was cervicitis and retroflexion of uterus. A dilatation and curettage, repair of the cervix and suspension of the uterus, and left oophorectomy was performed. This normal-sized ovary measured 3.5 by 2.3 by 2 cm.; it was removed because of a fibroma that measured 1 by 1.5 by 1.7 cm.

CASE 6.—Pseudomucinous papillary cyst adenocarcinoma. (Fig. 6.) Mrs. E. P., aged 64 years, was operated upon because of a pelvic mass found during a periodic examination. Preoperative diagnosis was carcinoma of the ovaries. She had a hysterectomy and bilateral removal. The large mass felt at pelvic examination was a large malignant papillary cyst. The apparently normal ovary which measured 4 by 2.5 by 1.5 cm. contained a small malignant cyst which measured 1.7 by 1.2 by 1.4 cm.

This patient had a cancer of the hepatic flexure four months previously for which she had a resection, at which time there was no evidence of ovarian malignancy. More than this, no evidence of ovarian enlargement was noted until very shortly before this operation for ovarian carcinoma, in spite of frequent examinations by a competent gynecologist. This case emphasizes the rapidity of growth of ovarian cancers. We have records of three other similar cases of rapid growth in which unfortunately periodic examinations revealed no enlargement until shortly before operation.

CASE 7.—Granulosa-cell tumor, folliculoid type. (Fig. 7.) Miss C. L., aged 23 years, was admitted because of vaginal bleeding. She had had two previous admissions, once when 14 years old, and again when 22 years of age, for vaginal bleeding. Dilatation and curettage was done each time, after which she was discharged with the diagnosis of functional bleeding. Preoperative diagnosis on the present admission was a pedunculated fibroid or ovarian tumor. The operation done was a dilatation and curettage, partial left salpingectomy, and a right salpingo-oophorectomy. This patient had a bilateral chronic salpingitis and a granulosa-cell tumor 3 mm. in diameter in a normal-sized ovary that measured 2.5 by 1.5 by 1.3 cm.

This case is extremely interesting because of the occurrence of a granulosa-cell tumor in a normal-sized ovary and the associated symptom of vaginal bleeding, intermittent, since her menarche. The patient has been followed since the operation four years ago and gives no indication of any further menstrual disturbance.

That not infrequently tumors in apparently normal ovaries can be detected at operation, as shown by this presentation, is important because it is an addition to our meager armamentarium in the effort to improve our results in the prevention of gross ovarian disease. If every surgeon carefully examined every ovary at every operation in which this is feasible, a certain number of very early neoplasms would be discovered that would otherwise be missed. As an example we can cite our own observations in our gynecologic clinic at the Graduate Hospital of the University of Pennsylvania in the past three years, in which seven tumors were found in ovaries that appeared normal. That this number of cases was found in one hospital, in fact in the gynecologic clinic alone, should emphasize the potentiality of this observation when we take into account the great numbers of clinics in this country.

Routine examination of ovaries in abdominal operations is performed inadequately in most instances. Examination of the apparently normal ovaries

should include inspection and careful palpation for areas of abnormal consistency, and if necessary aspiration with a needle. Even incision may be done, as it will do no harm in a suspicious case and may save future embarrassment. The routine puncturing of small follicle cysts for the purpose of diagnosis is to be recommended; an occasional neoplasm will be discovered by this procedure.

Special attention should be given to the examination of the apparently sound ovary in patients operated upon for unilateral ovarian growths. This is important because of the bilateral tendencies of many tumors; in such cases the apparently normal organ is more apt to harbor a small neoplasm that gives no obvious evidence of its presence at the time of operation.



Fig. 7.—*a*, M' = low power of a node 3 mm. in diameter of granulosa cells in an ovary that measured 2.5 by 1.5 by 1.3 cm. (other collections of granulosa cells here and there). *b*, High power showing the granulosa cells. They are largely swollen and clear due to lipid deposition. The folliculoid arrangement of the cells can be seen.

If a minute growth is discovered in a normal-sized ovary during the course of an operation, and it is deep-seated and its nature is questionable, removal of the entire ovary is indicated because tumors of a malignant nature are more apt to be deep-seated. However, complete removal of an ovary is often unnecessary. Ovarian fragments can often be conserved, especially when the lesions encountered are simple cysts or dermoids. As a rule the tissue near the hilus is found to be normal and its blood supply adequate. Even if the circulation of the ovarian fragment is somewhat impaired, it may later become vascularized. In conserving an ovarian fragment one should be sure to remove the entire tumor, and care should be taken in suturing the ovarian remnant, for if there is great vascular damage from the suturing, retention cysts may result.

Summary and Conclusions

That some of the tumors which occur in apparently normal ovaries can be detected at operation is shown by our presentation of seven cases of neoplasms in ovaries that were of normal size. These tumors were found in the past three years in one clinic (Gynecological Clinic of the Graduate Hospital of the University of Pennsylvania); if the many clinics in this country in which abdominal operations are done made a special effort to examine all normal-sized ovaries with extreme care, which means inspection, palpation, puncture, and even incision of the ovary if necessary, our percentage of positive findings of pathology in normal size ovaries would be equalled if not exceeded.

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1930 CHESTNUT STREET

THECA-CELL CYSTOMA OF OVARY

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IN THE past several years an ever increasing number of theca-cell tumors of the ovary have been recorded in the literature, all of essentially similar character. They have been properly designated as solid estrin-producing neoplasms having the appearance of fibromas. Small cystic areas have been observed in a few instances (Novak, McGoldrick and Lapp). The cyst formation in the latter few cases were attributed to liquefaction necrosis of the neoplastic tissues. In the past six years, however, of a total of ten theca-cell tumors observed at New York City and Lincoln Hospitals, two cases were studied which warranted their designation as theca-cell cystomas. In both instances cyst proliferation was noted.



Fig. 1.—Case 1. Cross section of ovarian tumor illustrating its solid fibrous gross appearance.

Case Reports

CASE 1.—S. K., a 30-year-old Negro woman, was admitted to the Gynecological Division, New York City Hospital, June 17, 1941, with the chief complaint of sharp, cramplike pains in the lower abdomen for three years prior to admission. During the same period, there occurred occasional episodes of dizziness, and a “pulling down” sensation in the lower abdomen three or four days before menstruation. There was an additional complaint of frequent nocturia. The gynecologic history revealed the onset of menstruation at 14 years



Fig. 2.—Case 1. Microsummar photograph of cyst cavity.

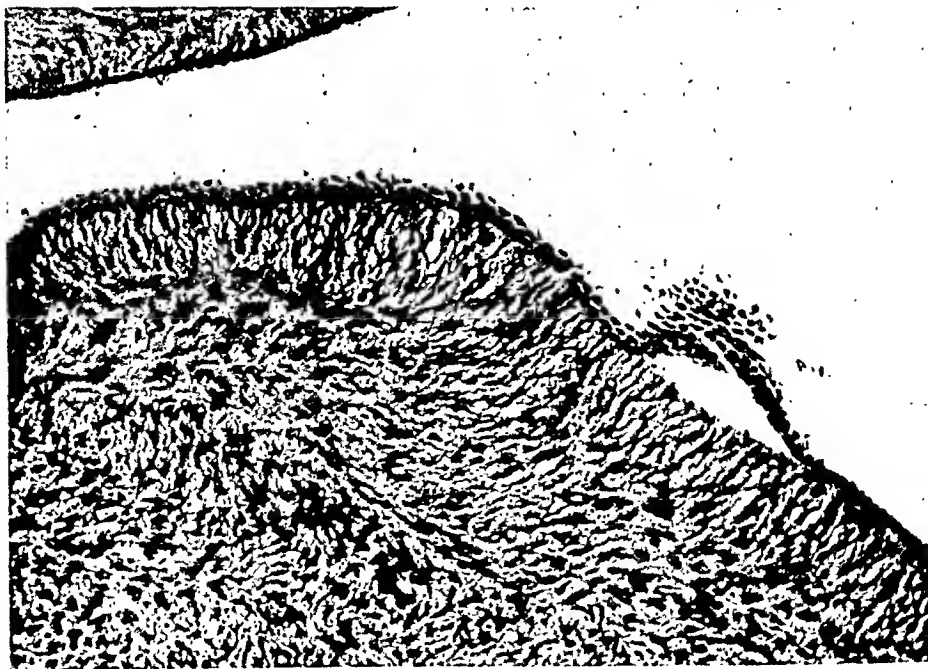


Fig. 3.—Case 1. High-power photograph of granulosa-cell lining of cyst cavity, and the theca-cell stroma.

of age, with regular 30-day intervals, of three to four days' duration. The patient was a gravida ii, para ii. For six months prior to hospital admission, menstruation had become irregular and prolonged, occurring every 22 to 26 days and lasting five to six days.

Physical examination revealed the patient well developed and well nourished. The blood pressure was within normal limits. A vague mass was palpable in the right lower quadrant of the abdomen. Vaginal examination revealed the uterus retroverted, somewhat enlarged, and irregular. A firm, large mass was palpated in the right adnexa. The mass was thought to be a pedunculated uterine leiomyoma.

Laboratory examinations were essentially normal.

Laparotomy performed six days after admission disclosed a large, firm, right ovarian mass, which was excised. The patient made an uneventful recovery and was discharged from the hospital on July 4, 1941.

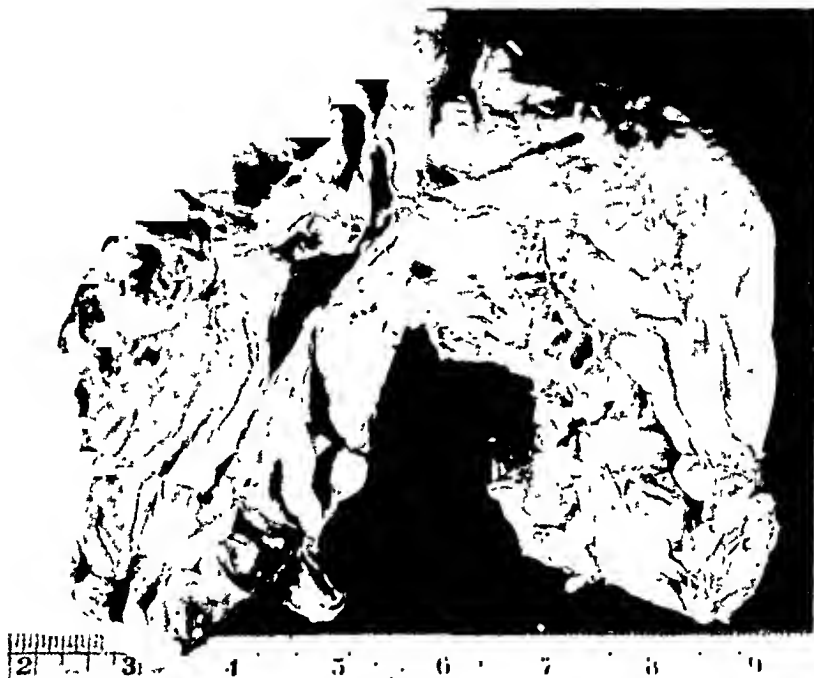


Fig. 4.—Case 2. Gross specimen photograph illustrating the large and small cyst cavities, and the irregular solid neoplastic areas.

Pathology.—The gross specimen was that of a markedly enlarged ovary measuring 7 by 7 by 6 cm. Several small, thin-walled, translucent cysts were noted in the cortical zone of normal ovarian tissue. On section, a well-circumscribed, round, firm mass measuring 7 cm. in diameter comprised the greatest part of the specimen. The cut surface presented a dense, fibrous appearance, with several irregular, pale yellow areas interspersed in the fibrous tissue.

Microscopic examination disclosed the mass well-demarcated from a thin zone of normal ovarian tissue. The latter contained several simple follicular cysts which were visible in the gross specimen. The tumor mass was composed of densely packed, large, spindle- or oval-shaped cells of fibroblastic appearance, in an irregular, interlacing pattern. A moderate-sized, cystic area was noted within the neoplastic mass. The cyst cavity contained a papillomatous structure, whose stroma had a myxomatous appearance. The entire cyst was lined by flattened euboidal epithelial cells. Similar cells in a single layer covered the papillomatous structure.

Sections stained by the Hoeff-Romeis technique as recommended by Tiaut and associates for the demonstration of inter- and intracellular estrogenic phospholipids gave a positive result. Silver stains revealed an abundant reticulum.

The final diagnosis was theca-cell cystoma.



Fig. 5.—Case 2. A, High-power view of cells lining the cyst cavities; B, low-power view of granulosa-cell nests; C, high-power view of theca-cell stroma in the irregular solid areas.

CASE 2.—S. L., a 59-year-old Negro woman, was admitted to the Gynecological Division, New York City Hospital, on Mar. 17, 1942, with the chief complaint of progressive abdominal enlargement of one year's duration. The patient stated that since first noticing the abdominal distention, the abdomen had markedly increased in size. There had been occasional sharp, "pulling" pain when doing housework. Marked urinary frequency was also noted.

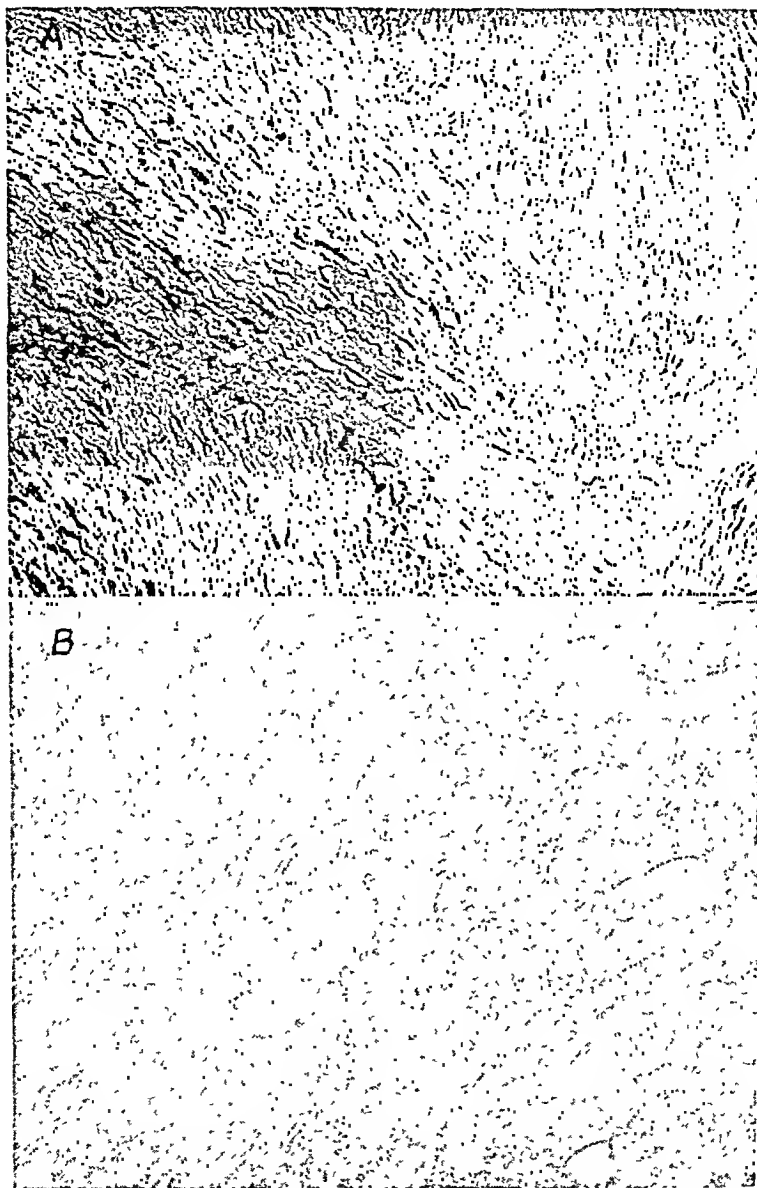


Fig. 6.—A, Representative section, silver stained, demonstrating reticulum; high power. B, Representative section, Hoerr-Romeis stain, demonstrating phospholipids; high power.

The gynecologic history revealed the onset of menstruation at 13 years of age, at regular 28-day intervals, and of four to five days' duration. The patient was a gravida vi, para vi, last gravid thirty years before. Menstruation ceased at 48 years of age. One year later, slight vaginal bleeding recurred at regular 28-day intervals, lasting four to five days. This continued for eight years when the bleeding episodes became prolonged and more profuse. For six weeks prior to admission, "spotting" was noted every day.

Physical examination revealed the patient well developed, and well nourished. The abdomen was uniformly enlarged to the size of a six months' gestation. A large cystic non-

tender mass was palpable to just above the umbilicus. On vaginal examination, blood was visible coming from the cervical os. The uterus was enlarged and could be palpated independently of the abdominal mass.

A preoperative diagnosis of possible pseudomucinous cystadenoma of the ovary was made. Laparotomy performed on March 27, 1942, revealed the uterus enlarged to the size of a three months' gestation, with several pedunculated masses arising from it. The Fallopian tubes were of normal appearance. The left ovary was enlarged to the size of a six months' gestation. The mass was cystic with a smooth opaque outer surface, adherent to the sigmoid colon and the uterus. In order to remove the mass, it was incised and its thin pale yellow fluid contents aspirated. Numerous large and small cyst locules were then encountered. A panhysterectomy was performed. There followed an uneventful recovery, and the patient was discharged on July 4, 1942.

Pathology.—The gross specimen consisted of a large nodular uterus, both normal-appearing Fallopian tubes, and a small, right ovary. A large cystic mass was noted arising from the left adnexa, firmly adherent to the left lateral aspect of the uterus. The uterine and cystic masses together measured 21 by 17 by 8 cm. The nodular uterus was enlarged. On section, several intramural myomata were noted, the largest measured 4 cm. in diameter. The endometrium was markedly thickened.

The thick-walled cystic mass measured 17 cm. in its greatest diameter. On section, the mass was multilocular. There were several large cyst cavities and many small thin-walled cysts giving a honeycombed appearance. The cavities contained a thin yellow fluid. Several large irregular, dense fibrous areas of pale yellow color were noted in the outer cyst wall.

Microscopic examination of sections of the cyst revealed the dense fibrous areas formed of closely packed spindle-shaped cells of fibroblastic appearance. The thin septa of the many small cyst locules were formed of similar cells. Lining epithelial cells were noted in several small areas only. These for the most part were cuboidal in shape with oval-shaped pyknotic nuclei. Few small, solid nests of granulosa-like cells were noted in the extensive fibrous areas. Stains for phospholipids were positive. Foot silver stains revealed an abundant fine reticulum.

Sections of the uterus revealed in addition to the leiomyomas, a typical "Swiss cheese" hyperplasia of the endometrium.

Sections of the Fallopian tubes revealed a marked hyperplasia of the epithelium. Sections of the right ovary revealed a small, well-circumscribed fibroma. Phospholipid stains in the latter were negative.

The final diagnosis was theca-cell cystoma.

Discussion

The observation of true cyst formation in two instances in tumors heretofore described as purely solid tumors lends support to the theory endorsed by Novak and Traut and others that the feminizing tumors of the ovary develop from early undifferentiated ovarian mesenchyme. In both instances recorded above, the lining epithelial cells of the cyst cavities were in appearance strongly suggestive of granulosa cells. Thus both granulosa- and theca-cell elements, fairly well differentiated as such, were present. In addition, Case 2 disclosed small, irregular nests of granulosa-like cells in the dense theca-cell stroma, an observation also made by Traut and associates, in a few instances in their series of cases. It is likely, therefore, that these granulosa-cell nests were the underlying cause for cyst formation in these tumors. The probability exists that cyst proliferation depends merely on the degree of differentiation of the granulosa cells.

Furthermore, special attention is called to the fact that as in Case 2, the cystoma may reach such large size as to be readily confused with other ovarian cystomas.

Summary

1. Two cases of theca-cell cystoma of the ovary are reported.

2. The observation of cyst proliferation in this type of tumor, heretofore only reported as solid tumors, lends support to the theory advanced that these tumors arise from early ovarian mesenchyme.

3. Attention is hereby called to the fact that these tumors may reach such large proportions as to be readily confused with other ovarian cystomas.

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GRANULOSA-CELL TUMOR WITH PREGNANCY FOLLOWING REMOVAL

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THE granulosa-cell tumor seems to possess some elusive interest and appeal shared by none other of the ovarian family. This is due to its ability to reawaken the attributes of youthful femininity by fanning into flame the dying embers of the sex gland of the postmenopausal female.

Rare though the granulosa-cell tumor may be, still more remote is mention of the occurrence of pregnancy following its removal. The literature records only three such cases, to which a fourth is now added.

The granulosa-cell tumor makes up about 2 to 3 per cent of all solid ovarian tumors, (Schröder). It appears most commonly in women about the menopausal age. Occasional examples are seen in younger women between puberty and the menopause, while a few have been found in children.

The clinical history of patients having one of these tumors depends primarily upon the fact that they possess endocrine activity, while mechanical and circulatory disturbances and occasional malignancy are accessory factors. The hypersecretion of estrin produces a characteristic syndrome associated with hyperplasia of the endometrium, irregular uterine bleeding, and gradual symmetrical hypertrophy of the musculature of the uterus.

In infancy and childhood the tumor usually produces precocious puberal phenomena with the onset of menstruation. With the removal of the tumor these symptoms retrogress completely, a crucial demonstration of the causative role of the tumor hormones in their production. (Indeed, in at least one recorded case in which such regression occurred, a second reappearance of the precocious symptoms was found due to a recurrence of the tumor in the other ovary. Removal of the recurrent growth was followed by a disappearance of the abnormal symptoms.)

After the menopause there is a recurrence of a more or less regular type of uterine bleeding, enlargement of the atrophic uterus, and occasionally a re-emergence of sex desire. Infrequently, breast atrophy is replaced by transitory hyperplasia. Curettage of the uterus reveals a cystic glandular hyperplasia of the endometrium in the majority of patients; however, a few instances have been seen in which the premenstrual or secretory type of endometrium was seen, even in women of advanced age.

During the period of sexual activity, the symptomatology due to the endocrinal potencies of the tumor is less noticeable because of the proximity of normal menstrual function and also because the other ovary, which is often normal, may serve to mask the picture. However, there is usually a period of amenorrhea followed by menorrhagia or metrorrhagia, or there may be simple irregularity of the menses.

In the amenorrhoeic stage, there may also be an associated hirsutism, male type of escutcheon and beard. Severinghaus' states "that in its ovarian aspects menstrual rhythm may be disturbed by alteration in the duration or intensity of follicular or luteal secretory activity."

If the tumor is benign, its removal served to re-establish the former stature of the patient, thus giving clinical proof of its endocrinal activity, except that in those prepubertal cases where the menarche is imminent, the individual may continue sexual development with more or less normal periodicity of the menstrual function.

Approximately 80 per cent of the granulosa-cell tumors are clinically benign. When malignant, they metastasize rapidly and produce death in a short time. P. J. Kearns² states that in his opinion, less than 5 per cent of granulosa-cell tumors are malignant.

It may be generally stated that while both granulosa-cell carcinoma and arrhenoblastoma are undoubtedly much less malignant than more common types of ovarian carcinoma, they must always be looked upon as potentially malignant, and in many cases the degree of clinical malignancy is high. Moreover, recurrence is sometimes extremely late, after intervals of ten or even eighteen years. Novak³ states that there does not seem sufficient justification for the rather light attitude of some writers toward this type of tumor, especially since histologic criteria have not been found to constitute a reliable index of the degree of malignancy.

When a benign granulosa-cell tumor takes control of the menstrual cycle in a young woman, sterility is to be expected, and this, no doubt, is usually the rule. Dr. Clair Folsome has personally recounted to one of us, however, a case where he found a pregnancy in association with a granulosa-cell tumor.

In this young type of woman, following removal of a benign granulosa-cell tumor, fertility and normal reproductivity should not be unexpected unless both ovaries have been removed. Even so, the literature mentions only three previous cases of this nature.

Klafton⁴ found pregnancy one year after a tumor was removed from a 29-year-old woman. This was followed by ten years of amenorrhea. Then a second tumor of the granulosa-cell type was removed from the opposite ovary.

Countiss⁵ reported a case of a 36-year-old woman who had profuse, almost continuous, menstrual bleeding, followed by amenorrhea. The uterus was enlarged to the size of a six weeks' pregnancy, and a curettage showed a grossly hyperplastic endometrium, while the ovary showed a tumor 4 by 3 by 3 cm. One year following removal of tumor, pregnancy occurred.

Schulze⁶ reported a case of a woman 27 years of age, with five years' sterility. Two years following removal of a granulosa-cell tumor in the ovary, the patient gave birth to a full-term child.

Case Report

The patient, Mrs. D. H., a 35-year-old woman of Anglo-Saxon origin, was admitted to the Women's Pavilion of the Royal Victoria in October, 1943, for excision of a palpable pelvic tumor associated with lower abdominal pains. The previous menstrual history was most unusual. From the menarche at 13 years of age, intermittent amenorrhea was noted, menstruation occurring at intervals of six weeks to six months. Two years after marriage she became pregnant and was delivered of a healthy child. She had only one period four months after delivery. During the next four years the patient complained of amenorrhea, fatigue, and nervousness. She gradually developed a nagging pain in the right lower quadrant and examination revealed a tumor replacing the right ovary. This was observed to grow from the size of a small egg to that of a baseball during the course of a year.

At operation, a solid grayish-white ovarian tumor was found on the right side, while the left appeared healthy. In view of the age of the patient and her desire to rear further offspring, the surgeon (W. R. F.) removed only the diseased organ. Postoperatively the patient menstruated only once before becoming pregnant. It is of interest to note that prior

to the operation the patient was in a very unstable state of mind, appearing restless and irritable, while sexually she had a total absence of libido. Since operation she has recovered from this confused state and sexual desires and relations have been normal.

The pregnancy progressed satisfactorily and she gave birth to a perfectly healthy child. Since delivery the patient has had a normal menstrual cycle of twenty-eight days and has enjoyed her first good health since the onset of puberty.

Pathologic Report.—Grossly, the ovary presents a round firm, grayish-white mass, measuring 7 by 5 cm. The cut surface presents a homogeneous whitish appearance with one small cystic cavity the size of a cherry in its center.

Microscopically, the cortex appears moderately thick, while spreading throughout the whole structure of the ovary are large solid masses of granulosa cells (Figs. 1 and 2). The cortex and hilum alike exhibit intensive infiltration and obliteration by clumps of these immature-appearing epithelial elements. No follicle or glandlike pattern is demonstrable, but numerous Call-Exner bodies are apparent.

Diagnosis.—Granulosa-cell tumor.

Comment

The initial impulse of the pathologist on diagnosing a unilateral ovarian mass as a granulosa-cell tumor is to query the fate of the remaining ovary, and to cast doubt upon the wisdom of the surgeon in leaving it. The subsequent course of the patient in promptly becoming pregnant would unquestionably justify the course followed. Even if a second granulosa-cell tumor should chance to develop in the remaining ovary in later years—and this possibility must always be borne in mind—the patient has meanwhile been rewarded by a normal healthy child which would have been lost if a radical bilateral oophorectomy had been performed to say nothing of the mental and physical effects which might result from a surgical castration.

An interesting situation arose when the clinician queried the pathologic report of the tumor as a "granulosa-cell carcinoma." There appeared to be ample reason to question whether this should be labeled as a "carcinoma" when the patient was already pregnant and the tumor was clinically, at least, proved to be relatively benign. Indeed, with the subsequent developments in the case, the pathologist considered it wise to redesignate the lesion as a "granulosa-cell tumor."

Long periods of amenorrhea in a so-called "feminizing" tumor where a large amount of secretion of the estrogenic hormone is believed present seem difficult to explain. Dr. J. S. Henry of our clinic is of the opinion that so long as the estrogenic level in the body is on the increase, amenorrhea will ensue. Whenever it becomes stationary or drops, then bleeding will soon follow. In this manner he feels that amenorrhea could persist up to six months or longer. Dr. G. B. Maughan supports the hypothesis that the excess amount of the estrogenic secretion acts upon the pituitary gland, depressing the gonadotropic hormone, resulting in amenorrhea. It is well known that one may knock out normal menstruation perhaps for some months by continuous administration of large doses of stilbestrol or other similar preparations.

It is noteworthy that three out of four of the cases mentioned here make definite mention of a prolonged period of amenorrhea, whereas bleeding is generally considered to be the clinical feature in tumors of this type.

In our case the surgical excision of the tumor was promptly followed by a clinically normal menstruation. It appeared that the removal of the conflicting endocrine force permitted rapid physiologic resumption of the normal sexual cycle, with prompt fertilization resulting in a pregnancy which carried on in a perfectly normal fashion to maturity.

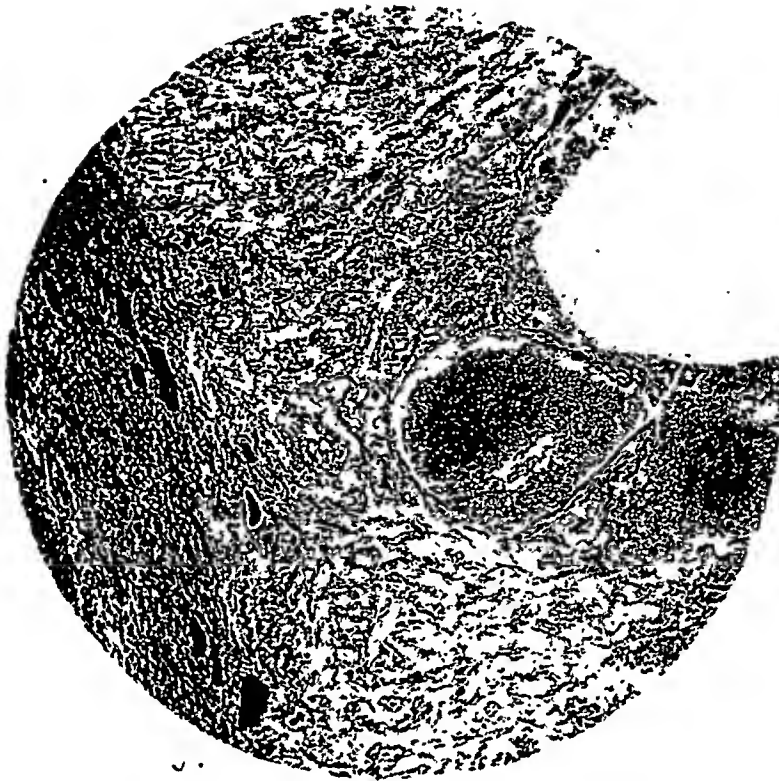


Fig. 1.—Granulosa-cell tumor. Low power taken near cortex. Note solid masses and infiltrating groups of granulosa cells.

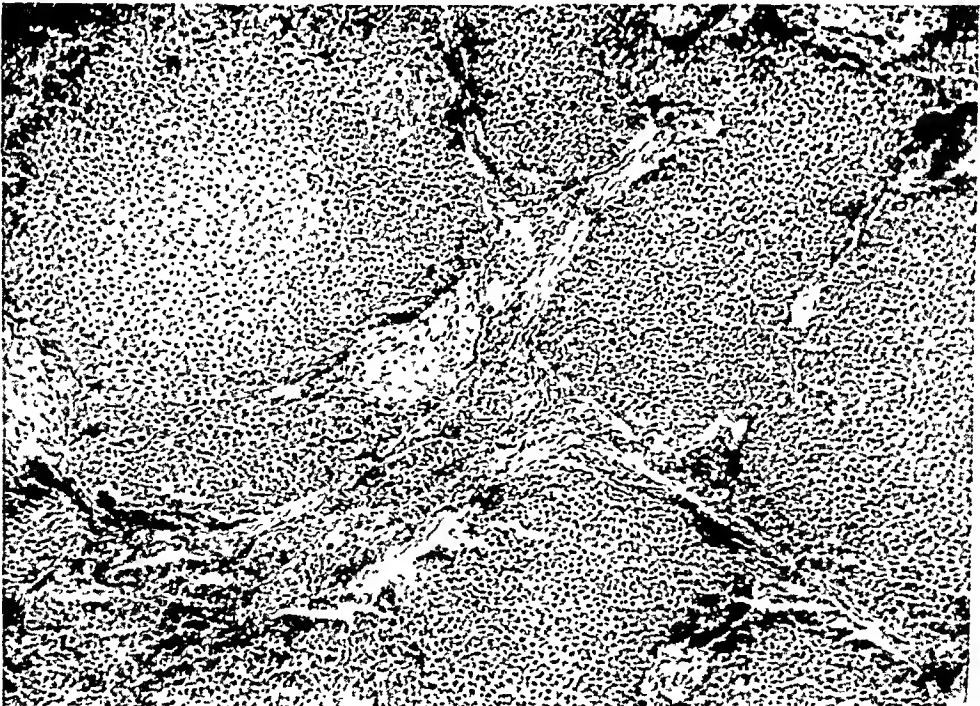


Fig. 2.—High power showing homogeneous appearance of sheets of granulosa cells replacing ovarian structure.

Conclusions

A case has been presented where a granulosa-cell tumor was removed from a young woman, to be followed by a normal pregnancy.

It would appear that conservative surgery is justifiable in sparing the second ovary when free from signs of malignant disease in a woman in the reproductive age.

Amenorrhea would appear to be a common clinical feature of granulosa-cell tumors occurring in a young woman.

The authors wish to acknowledge with thanks the assistance of Dr. Marion Francis in preparing data for this paper.

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AN EARLY OVARIAN PREGNANCY*

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SINCE the possibility of ovarian pregnancy has been recognized, something over seventy cases have been reported. A critical examination might reduce this number somewhat. It is probable that some escape notice, and that the actual number is greater than we may believe. The number of reported cases is still sufficiently small that it is of interest to add to the number.

A woman 30 years of age entered the hospital July 1, 1944, suffering from lower abdominal pain. Her last menstrual period was June 1. She had had no children but had aborted once. Some hours before admission she had sudden cramplike abdominal pain which recurred at intervals. There was no vaginal bleeding. She fainted once about two hours before admission.

On admission she was in fair condition; pulse 100, and leucocytes 12,000. Bimanual examination disclosed a mass on the left side which was quite tender and much smaller than is often found in tubal pregnancy. A diagnosis of ectopic pregnancy was made, and operation carried out at once.

A large amount of blood was found in the abdomen. The left tube was entirely normal. When the fimbriated end was wiped off, no blood was seen coming from it. The left ovary contained a small cystic mass about 3 cm. in diameter. This was entirely free from the tube. The relationship of the ovarian ligament to the ovary and the cystic mass was quite clear and was quite normal. On the surface of the small cyst farthest removed from the ovary was a dark red area from which active bleeding came. This mass was removed from the ovary with little difficulty and the resulting wound closed with sutures of fine catgut. Recovery was uneventful. The adnexa on the right side were entirely normal. The excised mass was placed immediately in Bouin's solution.

Many sections were made through the area from which the bleeding came.†

The greater part of the wall of the cystic mass was made up of corpus luteum cells. The follicle had evidently discharged the ovum a sufficient time before the operation that luteinization had had time to take place. At the area of hemorrhage were found masses of cells which were definitely different from the cells of the greater part of the wall. An area of hemorrhage was seen, around which were groups of large cells with deeply staining nuclei. These cell masses were evidently parts of what^a had originally been a much larger mass which had been broken up by hemorrhage. These cells we believe to be cells of proliferating trophoblast, largely syncytial cells. Dr. Leslie B. Arey agreed with us that the cells are syncytial in character and that they undoubtedly indicate an early pregnancy.

As the tube was wholly normal, it is evident that the implantation was not a secondary one. The egg, after fertilization, attached itself to the follicle from which it had shortly before escaped. It is possible that the ovum entered the ampulla of the tube and escaped again without implantation in the tube, and that it then attached itself to the ovary. The attachment was to the outer surface of the follicle and the development of the ovum was hindered by the fact that it had attached itself to a surface unfavorable for growth.

As the normal tube was not removed, it is impossible to state whether a decidual reaction was present or not. It is probable that much of the cell mass which existed before the onset of hemorrhage was swept away by the flood of blood. The remaining cells resemble strongly those seen in an embryo of the Rock-Hertig series of about ten to twelve days.

*Presented before a meeting of the Chicago Gynecological Society Dec. 15, 1944.

†Dr. John McCarter, assistant professor of pathology at Northwestern University, and director of the Abbott Memorial Laboratory, devoted much time and skill to the preparation and study of microscopic preparations.



Fig. 1.—Early ovarian pregnancy showing central hemorrhage ($\times 43$).



Fig. 2.—Higher magnification showing syncytio-trophoblast ($\times 215$).

While the size of the pregnancy seems smaller than would correspond with the length of time which elapsed between the last period and the date of bleeding, this would seem to be accounted for by the fact that the ovum was trying to grow in an inhospitable field which would cause development to be slower than that of a normally placed ovum. The pregnancy is smaller than any which I have been able to find among the reported cases.

In many of the reported cases the fertilized ovum developed in the cavity of the follicle. Veit has pointed out that the attachment of the ovum is not necessarily within the follicle. In this case it attached itself to the outer surface of the ovum from which it had escaped. The conditions laid down by Spiegelberg for recognition as an ovarian pregnancy are met in this case.

HYDRADENOMA AND HYDRADENOID CARCINOMA OF THE VULVA*

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TUMORS originating in the sweat glands of the vulva are of particular interest. The sweat glands of the vulva include, in addition to the common or eccrine sweat glands, a special group called the apocrine glands. These glands are found in other parts of the body besides the vulva, and they give off an odor which, in lower animals, is often associated with sex scent. In human beings, the apocrine glands are more active during menstruation and pregnancy.

The rarity of tumors of apocrine glands, according to Gates, Warren, and Warvi,¹ is probably due to the fact that they have been included in reports with tumors of the ordinary or eccrine sweat glands. In their report of 94 tumors, there were 8 of apocrine gland origin, and 6 of these were from the vulvar region. The terminology has been further confused since many of these tumors have been considered malignant. McDonald² reported 30 such cases as adenocarcinoma despite the fact that there was no evidence of metastasis in the entire group.

Following the classification of Gates, Warren and Warvi,¹ the benign tumor of apocrine gland origin is called hydradenoma papilliferum, and the malignant tumor is called hydradenoid carcinoma. In this paper an example of each type of tumor is presented.

CASE 1.—Mrs. M. M., a white woman, 34 years of age, was admitted to the hospital in February, 1943, with numerous complaints, none of them referable to a small cystlike structure on the left labium majus midway between the anterior and posterior commissures. This was thought to be a sebaceous cyst, and the patient had been aware of it for over a year. This mass was removed as an incidental procedure during the operation for her major complaints. Grossly it measured 1 cm. across, when incised, and microscopic examination showed it to be a small tumor mass (Fig. 1) composed of two types of epithelium, one a tall columnar pink cell and the other a cuboidal, dark, blue-staining cell (Fig. 2). Both types of cells formed glandular arrangements with papillomatous infoldings. The entire tumor was surrounded by connective tissue and showed no evidence of invasion. Compound granule cells were seen in the lumina of some of the glands. The tumor was located immediately beneath the surface epithelium. A diagnosis of hydradenoma papilliferum of the vulva was made. There has been no recurrence of the tumor up to the present time, twenty-six months later.

CASE 2.—Mrs. A. C., a white woman, 67 years of age, was admitted to the hospital with the complaint of slight vaginal bleeding and purulent discharge for two weeks. Examination showed an ulcerated area overlying the Bartholin gland just within the vaginal introitus on the left. The region underlying the ulcer was indurated but no definite mass could be felt. A small portion of the tissue from the ulcerated area was removed for biopsy. Microscopic examination showed a growth which was rather superficial in places. It was composed of small deep-staining cells which grew in solid sheets and showed distinct evidence of invasion (Figs. 3 and 4). Mitotic figures were numerous but the growth was not pleomorphic. Small areas

*Read before the Pittsburgh Obstetrical and Gynecological Society, April 2, 1945.

resembling attempted pearl formation were seen. A diagnosis of hydradenoid carcinoma of the vulva was made. Following simple fulguration with cauter, the tumor has persisted, but there are no evidences of regional or distant metastases.



Fig. 1.—Hydradenoma papilliferum ($\times 10$). Note the well-encapsulated tumor just beneath the epithelium. The papillary arrangement of the growth is shown.



Fig. 2.—Hydradenoma papilliferum ($\times 270$). The cells in the left half of the picture are tall and pink staining with the nuclei toward the center of the cell. The right half of the photograph shows low cuboidal deeply staining cells.

Discussion

According to Novak,³ 40 cases of hydradenoma of the vulva had been reported before 1940. Since then, approximately an equal number of these tumors has been reported.^{1, 2, 4-6} The majority of these were found to be located on the labium majus, or at the fissure between the labia majora and minora. They are nearly always single. Grossly the tumor is usually under 1 cm. in diameter and is considered most often a sebaceous cyst. It is usually buried rather deep under

the skin, but may be pedunculated. These tumors may be of the solid adenomatous type, but are more often papillary in nature. The individual cells are usually of the columnar type. The nuclei are round and commonly lie one-third of the distance up from the basement membrane. The papillary type tumors contain little stroma.



Fig. 3.—Hydradenoid carcinoma ($\times 80$). This is the largest island of tumor found in the excised tissue. Note the invasive tendency of the growth and the pale areas vaguely resembling epithelial pearls.

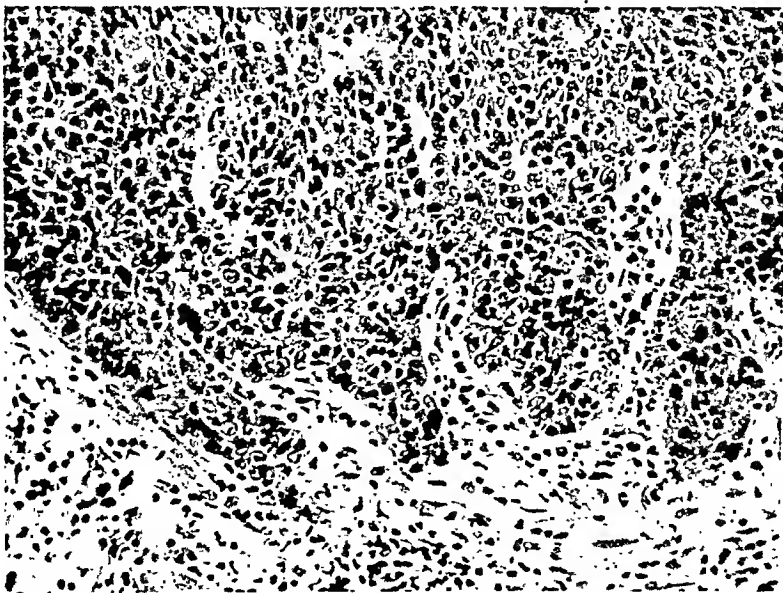


Fig. 4.—Hydradenoid carcinoma ($\times 270$). The cells show little cytoplasm, slight pleomorphism and a few mitotic figures.

The malignant tumor arising in the sweat glands of the vulva is the hydradenoid carcinoma. This tumor is, of course, not confined to the vulva, being seen anywhere on the body surface. Gates, Warren, and Warvi,¹ after reviewing the literature and including six cases of their own, list only 36 hydradenoid car-

einomas in which the diagnosis is definite. Of these, only five were tumors of the vulva. The information regarding such tumors of the vulva, what little of it is available, is indeed confusing. The writers are only in agreement on the point that these tumors are of low malignancy. The tumor reported in this paper is considered malignant and the diagnosis of hydradenoid carcinoma is made chiefly by exclusion. Despite the presence of areas resembling attempted pearl formation, this is not a keratinizing tumor. Pearl formation has been reported in a few hydradenomas of the vulva.³ Further, atypical pearls have been described in other nonkeratinizing tumors, such as hair matrix carcinoma and adamantinoma.

In the differential diagnosis, extension from the cervix must be considered. In this patient, the cervix was entirely free of tumor. The cells were too small and densely arranged to have originated in Bartholin's glands or from the sebaceous glands. Paget's disease and hair matrix carcinoma must also be thought of, but this tumor fails to show the characteristic histology of either lesion. The location of the tumor just inside the introitus is contrary to the described location of apocrine, or any other type of gland. However, it has been proposed that the hydradenoma at times develops from aberrant glands.⁴ On the other hand, it seems likely that this tumor may have extended to this location from the surface.

Summary

1. Hydradenoma papilliferum and hydradenoid carcinoma have been discussed and an example of each has been presented.

2. These tumors represent the benign and malignant phases of new growths arising in the apocrine glands of the vulva.

Thanks are due to Dr. Joseph A. Hepp and Dr. James Hodgkiss for permission to use the material.

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EXTENSIVE VARIX OF VULVA AND VAGINA IN FULL-TERM PREGNANCY; DELIVERY BY CESAREAN SECTION*

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ALTHOUGH varicosities of the vulva complicating pregnancy and labor are not uncommon, a varix of the vagina alone or in combination with those of the vulva is a rare lesion.¹ Mathieu and Holman² stated that in a combined obstetric experience of thirty-seven years they never encountered a vaginal varix. Such genital varicosities may give rise to considerable hemorrhage should they rupture in the course of labor.^{1, 3, 4, 5} Although DeLee⁶ states that such varicosities may be fatal from internal hemorrhage or from infection with complicating sepsis, the only treatment suggested is immediate suture or firm tamponade.

The European literature on this subject is much more revealing. Salvini's patient⁷ was a multipara, 29 years of age, who suffered rupture of a vaginal varix in the seventh month of her fourth pregnancy. She was sent into the hospital by her local physician with a diagnosis of central placenta previa. Examination demonstrated a ruptured vaginal varix as the source of bleeding, which was then controlled with two catgut sutures, and the patient was delivered spontaneously at term. In his case report Salvini mentioned that he witnessed a delivery in which rupture of a varix took place from the vestibule during delivery of the head and that in spite of the use of mass ligatures the patient died. In Constandulaki's case,⁸ forceps were applied to a vertex in persistent right occiput posterior position five hours after complete dilatation with, to use the words of the author, "a certain amount of apprehension because of great varicosities completely masking the vulva orifice." Following delivery, tremendous vulva bleeding occurred which was controlled by tamponade and hemostats. Frank⁹ mentions Kaufman's citation of a case where air embolism occurred through the site of a ruptured vaginal varix. Pestalozzi, Mahmmacher, Tarnier, and DuBois are cited by Salvini as having reported deaths following rupture of genital varicose veins. Naujoks¹⁰ states that abdominal section is the method of choice when large vulval or vaginal varicosities complicate pregnancy.

The following case is reported for three reasons: (1) To cite the case for the record, (2) To indicate the dangers of vaginal delivery in the presence of extensive genital varices, (3) To emphasize that in the presence of such extensive genital varices treatment of choice is elective cesarean section.

Case Report

A 23-year-old, white woman, married one year, registered at the Pre-Natal Clinic, Regional Hospital, Fort Monmouth, New Jersey, in the fourth month of her first pregnancy. Amenorrhea had been present since Feb. 10, 1943; it was expected that her date of confinement would occur about Nov. 20, 1943. The menstrual periods had always been regular with age of onset at 14 years, moderate five-day flow recurring at 28-day intervals. On physical examination, the patient was found to be well-developed, weight 118 pounds, height, 62 inches, blood pressure 100/62. Positive findings revealed a normal intrauterine gestation of four months' duration. Pelvic mensuration was adequate, gynecoid type. Blood serology test for syphilis was negative, urinalysis normal, erythrocytes numbered 4,750,000 per c.mm. with 90 per cent hemoglobin, leucocytes numbered 8,400 per c.mm. with normal differential.

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†Stationed at Rhoads General Hospital, Utica, N. Y.

At a scheduled prenatal visit toward the end of her sixth month, the patient complained of swelling of legs with pain in the left leg and aching in the vagina. Examination of the lower limbs revealed pitting edema and moderately severe varicose veins, more pronounced on the left leg. Vaginal examination demonstrated considerable vulval swelling with extensive bilateral varicosities of the labia majora and minora. Bulging through the vestibule at its lower angle for a distance of 1 cm. was a large, soft, purplish, nontender varicose vein, 2 cm. in diameter, which extended along the right margin of the posterior vaginal floor for a distance of approximately 5 cm. Because of these findings, the patient was instructed to wear an Ace bandage on the left leg, rest moderately during the day, and refrain from any type of exertion and further intercourse. As pregnancy continued, the genital varices in turn became more pronounced and the vaginal varix assumed a port-wine color. Fearing rupture of the genital varices with resultant hemorrhage if she was permitted to go into labor, an elective abdominal cesarean section was selected as the method of delivery. Throughout the entire prenatal period the blood pressure remained within normal limits, the urine was persistently normal, and the weight gain amounted to 27 pounds.

The patient entered the Regional Hospital, Fort Monmouth, New Jersey, on Nov. 10, 1943, for cesarean section. Abdominal examination on admission was as follows: height of fundus, 26 cm.; presentation, vertex; position, right occipitoanterior; fetal heart right lower quadrant. Admission laboratory study revealed a normal urinalysis; red blood cells, 3,400,000 per c.mm.; white blood cells, 11,600; hemoglobin, 66 per cent; blood type, O. On November 12, under ether anesthesia, a low classical abdominal section was performed with delivery of a normal living male infant, weighing 7 pounds, 1 ounce. Since the patient was not in labor and it was desired to complete the operative procedure with a minimum loss of time and blood, the classical method of cesarean operation was employed. The patient was in very satisfactory condition upon her return to bed but to maintain fluid balance 1,000 c.c. of 5 per cent glucose in normal saline was administered by vein. Because of the presence of a moderate secondary anemia, transfusion with 500 c.c. of citrated blood by the indirect method was performed upon recovery from the anesthetic. Other than a mildly severe atelectasis of the base of the left lung which manifested itself on the second and subsided on the fourth postpartum day, convalescence was uneventful until the twelfth day when she was permitted to dangle her legs. Pelvic inspection on that day revealed complete subsidence of the vulval varicosities and edema and considerable reduction in size of the vaginal varix, which appeared pale. That evening, left saphenous phlebitis developed, characterized by pain and fever. Treatment in addition to bed rest consisted of three x-ray exposures to Scarpa's region of the left thigh at three-day intervals, with dosage regulated at 50 roentgens filtered through 3 mm. aluminum. Following the second exposure there was complete freedom from pain and tenderness, and on the 26th postpartum day, fourteen days after the inception of the complicating phlebitis, the patient was discharged from the hospital.

She returned for postnatal examination six weeks after delivery. No varicose veins of the vulva or vagina were noted on examination. The uterus was anterior, nontender, regular in outline, and palpable one fingerbreadth above the symphysis. No adnexal tenderness was present. The abdominal scar was firmly healed, the thigh and legs showed only an occasional fine varicose vein.

Summary

1. A case is reported of a 20-year-old primipara whose pregnancy was complicated by extensive varicosities of the vulva and vagina.

2. The increased hazard of vaginal delivery in such cases is indicated by citation of case reports and references to the literature.

3. The treatment of choice for extensive genital varices complicating pregnancy is elective cesarean section.

4. A complicating postpartum phlebitis of the left saphenous vein was treated by x-ray therapy.

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TOXEMIA OF PREGNANCY WITH UNUSUAL POSTMORTEM FINDINGS

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CASE 1.—C55522, L. B., aged 25 years, a white woman, was admitted to the obstetric service of this hospital on Oct. 27, 1944. She was a gravida i, para 0, six months pregnant, and the date of the last menstrual period corresponded to the size of the uterus. The past personal history revealed a normal course during the first four and one-half months of the present pregnancy. In the course of the five to six weeks preceding hospital admission there had developed progressive weakness, occasional nausea and vomiting, inordinate thirst, excessive desire for water, polyuria, and on several occasions during this period she had passed what appeared to be small urinary calculi. No medical investigation of these symptoms had been undertaken by her physician. On the advice of a second physician, hospitalization was effected at once.

Conjoint admission examinations by an urologist, internist, and obstetrician disclosed an acutely ill primigravida with a flushed appearance, dry lips, and moderate exophthalmos. The temperature was 98.6° F. The heart sounds were of poor muscular quality, regular, rate 108. She was in a state of collapse, intermittently disorientated, and her blood pressure was 64/48. The internist thought the left kidney palpable and the right not palpable. There was no anuria, 21 ounces of urine being obtained by catheterization. Occasional twitchings observable in her face were considered of uremic causation. Fetal heart tones were regular, 144, in the right lower quadrant. The consensus was that the patient's condition was too grave to warrant investigation by x-ray, cystoscopy, etc., or induction of labor.

The diagnosis was uremia due to pyelonephritis. Polycystic disease of the kidneys was considered. Circulatory stimulation, intravenous glucose injections, penicillin, and other supportive measures were administered. All these were maintained for the next three or four days, until Oct. 31, 1944, when she was delivered in a stuporous condition, after artificial rupture of the membranes and a short labor, of a six months' living female infant which expired four hours later. A brief interval of about two hours of apparent improvement that followed delivery soon gave way to a comatose state in which the patient expired eighteen minutes after her fetus (Nov. 1, 1944).

On Oct. 28, 1944, hemoglobin was 85 per cent; on October 31, it was 118 per cent; red blood cells, 6,040,000; white blood cells, 23,200; polymorphonuclear, 94; staff, 26; segmented, 68; lymphocytes, 3; mononuclears, 3. Blood chemistry findings on October 27 were: glucose, 116; urea nitrogen, 150; creatinine, 3.0. On October 30, urea nitrogen, 180; creatinine 4.5. The temperature was 98° to 99° F., from the time of admission on October 27 until November 1 when it showed a premortal rise to 103.6° F. The blood pressure varied between 64/48 on admission and 48/20 on her last day.

A complete postmortem examination was made. Of particular interest are the kidney findings, which follow:

“Both kidneys are palpated and are felt to resemble bags filled with stones. Parenchyma is relatively thin. Calculi can be felt to move beneath the palpating fingers. Both kidneys are approximately equal in size. The left kidney measures 12 by 6 by 3.5 cm. and weighs 150 grams. The capsule strips easily exposing a smooth pink cortical surface. On section, the greater part of the kidney is seen to be occupied by numerous calculi varying in size from a pinhead to a small grape. They are all brownish in color and have a pumicelike appearance. There are approximately 1,000 stones in each kidney. The calices are dilated and many of the calculi lie in little pools of pus which tend to be confluent. The cortex and pyramids

comprise a relatively thin wall, measuring 5 to 10 mm. in thickness. They are poorly differentiated from each other. The color is pink. Serial section through the kidney results in finding calculi usually of pinhead size deep in the parenchyma. Stones are found in the pelvis of the kidney and gravel is found in the upper portion of the ureter. The ureter is unobstructed and of constant caliber throughout.

"The right kidney has the same measurements approximately as its fellow and presents a picture quite similar.

"Pelvic organs: The bladder contains a few cubic centimeters of urine. Its wall is thin. The mucosa shows focal areas of injection, but no ulceration.

"The uterus and adnexa weigh 670 grams. The former is the size of a six months' gestation, and is thick and boggy. The endometrial lining is ragged and hemorrhagic, having recently been deprived of the placenta.

"The other postmortem findings are not noteworthy.

"Pathological diagnosis: Bilateral obstructive calculous pyonephrosis with uremia associated with pregnancy; puerperal uterus; splenomegaly and hepatomegaly due to chronic passive congestion, hypostatic congestion of the lungs.

"Cause of death: Calculous pyonephrosis with renal insufficiency."—*J. M. Ravid, Pathologist.*

A direct postmortem radiograph of both kidneys, demonstrated at the general staff conference of this hospital, was of striking appearance due to the myriads of calculi.

This case demonstrates the possibility that massive calculous disease of both kidneys may by its insidiousness escape clinical recognition. Pregnancy was contraindicated and its continuance doubtless hastened the inevitably fatal uremic outcome. The futility of any therapeutic measures is emphasized by the postmortem findings without which the hopelessly pathologic condition of the kidneys would not have been determined.

CASE 2.—C51309, B. L., a white woman, aged 25 years, housewife, was admitted to the hospital on Dec. 25, 1943, because of pre-eclampsic toxemia. Her last menstrual period began on May 28, 1943, and the size of the uterus substantiated a six and one-half months' gestation. The first four months of pregnancy were normal. During the fifth month she travelled out of town, gained 14 pounds, and her blood pressure rose from 110/76 to 155/90. She stated that there was no albuminuria. Dietary restriction had been advised. In the course of the next week she gained 9 pounds more, making a total gain of 23 pounds in the past five weeks. She then returned to this city. Examination disclosed marked generalized edema, distorted facies, blood pressure 178/86, and 4 plus albuminuria. She was hospitalized the same day.

Hospital admission examination confirmed these findings and showed also a regular fetal heart rate of 140 above the symphysis. A pre-eclampsic medical regimen was instituted with the intention of inducing labor if a satisfactory response was not obtained.

In the course of the next three days (December 26, 27, and 28) improvement apparently followed. The edema lessened, being almost gone in the legs, the blood pressure declined to 150/86, the fetus continued viable, subjective improvement was noted, but albuminuria persisted at 3 plus. The next day, however, the blood pressure rose to 176/100, but the edema was still less. On December 30 and 31 the blood pressure rose to a height of 184/108, the edema, particularly in the face, increased, and the albuminuria remained at 3 plus. On the latter date she complained of severe heartburn and several times vomited a dark-brown fluid and blood. Induction of labor, therefore, was attempted that day by rupturing the membranes, inserting an intrauterine tube, and packing the vagina. The next day (Jan. 1, 1944), after several hours of irregular contractions, active labor was in progress. The tube and packing were removed. Profuse coffee-ground vomitus was noted several times that day. On January 2, while in active labor, an initial convulsion occurred at 4:45 A.M., to be followed by a second at 6 A.M. Her blood pressure at the time was 182/120, breathing stertorous, and coma persistent between seizures. Rectal examination showed the cervix 1 finger dilated, head at spines, and the anal sphincter patulous. Her general condition was not very good. At 8 A.M. she was still comatose and minor convulsive movements occurred repeatedly.

Uterine contractions recurred at two- to three-minute intervals. Her pulse was scarcely perceptible. Despite adequate morphinization, a third severe convulsion at 8:15 A.M. supervened. Suddenly she became extremely pale and, within fifteen minutes, expired.

Neither the hematological nor blood chemistry reports are informative. As in Case 1, a complete postmortem examination was made. The findings pertinent to the toxemia are unusual and only these are submitted:

"The abdomen is enlarged by a pregnant uterus corresponding to about six and one-half months' gestation. On vaginal examination the cervix is found to be 2 fingers dilated. The presenting part is engaged. On opening of the peritoneal cavity free and clotted blood is found in the abdomen, the amount being estimated to be about 500 c.c. The uterus and adnexa are carefully inspected and present no bleeding point. After removal of the blood, the liver surface presents a most remarkable picture. Over the left lobe, the capsule is somewhat lifted off the liver surface by a large palm-sized subcapsular hematoma. At one point near the liver margin the capsule is broken and blood oozes into the abdominal cavity. The rest of the liver surface is diffusely covered by confluent hemorrhages, giving the liver surface a yellowish, dark-red, mottled appearance.

"The liver weighs 1,120 grams as previously described, Glisson's capsule over the left liver lobe is lifted off the liver parenchyma by a large subcapsular hematoma, and at one place near the left lower liver margin, the capsule is broken and permits the subcapsular accumulation of the blood to ooze into the abdominal cavity. Scattered over the liver surface other much smaller hematomas (partly confluent but not attaining more than pea size) are seen. The liver parenchyma itself shows its original yellowish-brown color practically wiped out by diffuse, confluent, hemorrhagic streaks, and plaques. The areas intervening between these hemorrhages are distinctly yellowish in color. On section, a similar appearance is seen on the cut surface. The usual lobulated architecture can hardly be made out as the picture is dominated by confluent hemorrhages with areas of yellowish necrosis interspersed.

"The serosal surface of the gall bladder is mottled with hemorrhages.

"The uterus is the approximate size of a watermelon corresponding to about six and one-half months' gestation. The uterine wall is intact. The uterus is opened anteriorly and a female fetus is delivered. The latter measures 40 cm. in length. The placenta is attached to the uterine fundus and shows grossly no evidence of infarction.

"Pathological diagnosis: Diffuse hemorrhagic necrotizing hepatitis, as seen in eclampsia gravidarum, massive subcapsular hemorrhage of the liver, gravid uterus with female fetus of about six and one-half months' gestation in situ, tubal nephrosis, focal myocarditis (toxic variety)."—*J. M. Ravid, Pathologist.*

Since profuse intra-abdominal hemorrhage originating in the liver as an immediate cause of death in eclampsia is rare, this case merits a report. The paramount value of the postmortem examination is obvious since massive subcapsular hematoma of the liver with perforation was not suspected ante mortem.

Appreciation is hereby acknowledged to Dr. William Cantor who referred the first case, to Dr. Harry Lichtman who referred the second, and to Drs. Joseph Rosenthal and Emanuel Salwen who saw the first case in consultation.

PREGNANCY COMPLICATING MULTIPLE SCLEROSIS

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IT IS a well-established clinical fact that multiple sclerosis is frequently made worse by pregnancy. Since more than 40 per cent of the recognized cases of multiple sclerosis occur in women, and since its incidence is highest in persons between the ages of 20 to 40 years, it seems reasonable to suppose that the condition would be observed not too rarely with pregnancy as a complicating factor.

The first comprehensive survey of the subject was published by von Hösslin.¹ It was his opinion that the condition underwent distinct exacerbation throughout pregnancy. The next report was published by Beck.² This author reported a series of 118 patients with multiple sclerosis, 40 of whom had borne babies. Five cases had been diagnosed as multiple sclerosis prior to conception, and all of these showed exacerbations during or immediately after pregnancy. Dimitz³ quotes an analysis of 445 cases of multiple sclerosis collected from the literature by Kortum. Pregnancy had an adverse effect in approximately 20 per cent of these cases.

The literature is singularly silent on the effect of multiple sclerosis on pregnancy, labor, and the puerperium. Peckham,⁴ citing two cases, says: "If the condition is far advanced or is progressing more rapidly since the onset of gestation, abortion should be advised. If the disease is in its early stages and shows no evidence of exacerbation, the pregnancy may be allowed to continue. The labor should be conducted in the most conservative manner." Birner⁵ reports a case of pre-existing multiple sclerosis where pregnancy produced an improvement in some of the neurological symptoms after delivery.

The following case is of interest because of the improvement of neurological signs after delivery.

Case Report

F. F., aged 37 years, white, married, gravida ii, para 0. In 1940, four months after an automobile accident, she developed gradual weakness and difficulty in walking. She began progressively to lose control of the coordinated movements of both legs. Neurological examination at that time (Dr. Nathan Savitsky) revealed the following positive findings: tongue deviation to the left, absent abdominal reflexes, spasticity and weakness of both extremities with a positive Babinski on the left side, bilateral nystagmus. Examination of the eyegrounds revealed bitemporal pallor. Laboratory findings were essentially negative. Serological tests for syphilis were negative.

Her condition remained stationary. In 1942 she had spontaneous miscarriage in the fourth month. Following this another neurological examination showed the same findings as before.

She first came under my observation in August, 1942. She was then three months pregnant. Her last menstrual period had been May 3, 1942, and her expected date of confinement, therefore, was Feb. 10, 1943. The neurological findings at this time were: marked nystagmus, intention tremor, absent abdominal reflexes, and spasticity and weakness of both extremities. Her prenatal course was unusually normal.

Labor started Feb. 2, 1943, at 2:00 A.M., and she was admitted to The Bronx Hospital (case No. 142608). Under a Gwaltney analgesia the cervix became fully dilated at 7:30 P.M. She was delivered by low forceps of a living 9-pound male child after one hour in the

second stage under ether anesthesia. The baby was perfectly normal. The postpartum course was uneventful and the patient left the hospital on the tenth day.

Three months later, a postpartum examination noted the following neurological changes for the better: nystagmus only slight in the lateral position, increase in strength on the left leg, intention tremor much less pronounced.

In March, 1945, two years following the delivery of her baby, she returned for a vaginal discharge due to an eroded cervix. Examination showed no progression in the neurological findings.

Comment

A case of pregnancy complicating multiple sclerosis is reported.

The occurrence of pregnancy was two and one-half years after the onset of the multiple sclerosis.

The neurological condition was improved following the delivery and has remained so for two years.

I am grateful to Dr. Meyer Rosensohn, Attending Obstetrician, The Bronx Hospital, for his helpful suggestions in the preparation of this report.

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1840 GRAND CONCOURSE

DYSTOCIA DUE TO PELVIC KIDNEY

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PELVIC kidney has long been recognized as one of the rare causes of dystocia. Huter,¹ in 1880, reported the first case in literature, and Cragin,² in this country, in 1898, reviewed five previously reported cases and added one of his own. Since then, many case reports of pelvic kidney have been published but the factor of dystocia is so rare as to merit the reporting of the following case:

A 20-year-old primigravida was first seen in the prenatal clinic of AAF Regional Hospital, Truax Field, Nov. 8, 1944. Her last menses occurred March 10, 1944, making the expected date of delivery Dec. 17, 1944. The past menstrual history was normal and the history of past illness was not remarkable.

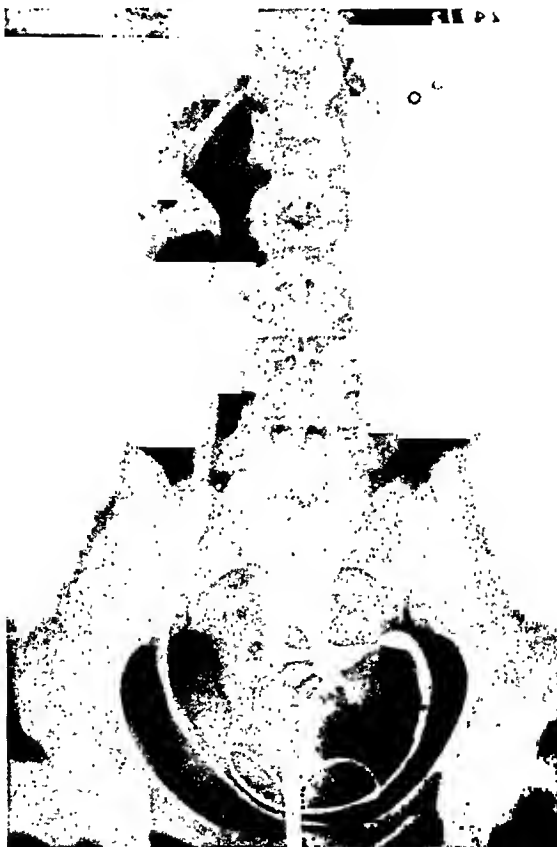


Fig. 1.

The general physical examination revealed no abnormalities. The fundus uteri was enlarged proportionately to that of thirty-four weeks' gestation. The presentation was sacral right anterior and the fetal heart tones were normal. The external measurements were compatible with a roomy pelvis; the outlet was normal. Since the pregnancy was but six weeks from term at the time of the first examination, no vaginal examination was done. The blood pressure, urine, and symptomatology remained normal during the follow-up examinations and the routine blood study showed no abnormalities.

The presentation remained breech during the remainder of pregnancy, and the patient went into labor Dec. 27, 1944. The pains were never very hard, but the cervix dilated nicely and, after ten hours, rectal examination revealed almost complete dilatation. The breech remained high, and a foot could be palpated through intact membranes. In the hollow of the sacrum could be palpated a firm, smooth, slightly lobulated mass which was interpreted as the buttocks of the baby. Because of an apparent delay in descent of the breech a vaginal examination was done. This revealed that the membranes were protruding through an almost completely dilated cervix. In the hollow of the sacrum could be felt a firm slightly notched mass which was fixed. The borders of the mass could not be outlined but it was estimated to be about the size of the fist. It was not part of the breech because the mass lay posterior and slightly inferior to the posterior margin of the cervix.

A tentative diagnosis of ovarian tumor in the hollow of the sacrum was made. It was decided that breech delivery from below was impossible because of encroachment on the pelvic cavity by the tumor. Accordingly, preparations were made for cesarean section. X-ray films revealed normal fetal skeleton with the fetus in complete breech presentation. The tumor could not be visualized. The fetal heart tones were good, the membranes intact.

A low cervical cesarean section was done under spinal anesthesia, because the patient had an upper respiratory infection. A normal baby girl, weighing 6 pounds 14 ounces, was delivered, and cried at once. After the uterine incision was closed, the corpus was delivered from the abdominal cavity and the cul-de-sac explored. In the hollow of the sacrum just below the promontory was a firm ovoid mass, slightly flattened, and attached at one edge. Its color was pale pink. The origin of the mass at first seemed obscure since both ovaries were normal. Palpation of the left renal fossa revealed no kidney present. It was assumed then that the mass in the pelvis was an ectopic kidney. The uterus was replaced and the abdominal incision closed. The postoperative course was entirely uneventful, the highest temperature being 99.4° F. The mother nursed her baby. On the tenth postoperative day a retrograde pyelogram revealed normal right kidney and ureter. The left kidney was visualized in the pelvic cavity (Fig. 1). The ureter was about half the normal length. Both kidneys had normal function with no evidence of infection. The mother and baby left the hospital on the fourteenth postpartum day in good condition.

Appreciation is expressed to Lt. Colonel Bernard B. Larsen, M.C., for his assistance in making the diagnosis of pelvic kidney at the time of operation, and to Captain William E. Forsythe, M.C., for the excellent pyelography.

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SUBCUTANEOUS THORACOPLASTY ON THE PARTIALLY DELIVERED IMPACTED FETUS: A SUBSTITUTE FOR EMBRYOTOMY

CHARLES G. BARNUM, M.D., GROTON, CONN.

*(From the Obstetrical Service of the Lawrence and Memorial Associated Hospitals,
New London, Conn.)*

A RATHER obese 39-year-old white para xii was admitted to the hospital in labor, June 7, 1944, about two weeks after the expected date of her delivery. Two years previously she had delivered a 9-pound baby spontaneously.

After a tedious labor, the very large fetus was delivered by breech extraction to a point where the lower thorax was out, but farther progress could not be made. So tightly did the fetus fill the birth canal that not even a finger tip could be introduced anywhere between the fetus and the walls of the canal. The fetus was dead.

Rather than take the fetus apart to accomplish its removal, a novel expedient was employed, an adaptation of thoracoplasty. Allowing the fetus to hang without support and using standard suture scissors, a two-inch incision was made parallel and close to the left costal border into the abdominal cavity. The first and middle fingers of the left hand were slipped between the skin and the thoracic cage up to the axilla, and then working the scissors between these two fingers the ribs were divided up to the axilla. The hand was withdrawn, and when pressure on the chest was made, it collapsed enough to permit introducing the hand far enough to reach the anterior shoulder of the fetus. With the assistance of a blunt hook the anterior arm and shoulder were brought out and then the other shoulder was delivered. The head was delivered with Piper forceps.

After delivery the baby weighed 12 pounds, $3\frac{1}{2}$ ounces and the thorax resumed its normal contour, with only a 2-inch incision at the left costal border.

The advantages of the procedure were:

1. Facility of execution, about five minutes from the start of the procedure to the completion of the delivery.
2. Avoidance of mutilation of the fetus.
3. The cut bones were completely covered by the undivided skin of the fetal thorax, so that neither the maternal soft parts nor the hands of the operator were damaged.

230 THAMES STREET

A NEEDLE SHIELD FOR CONTINUOUS SPINAL ANESTHESIA DURING LABOR AND DELIVERY

SYLVAN M. SHANE, D.D.S., CAMDEN, N. J.*

(From the Department of Anesthesiology, West Jersey Hospital)

CONTINUOUS spinal anesthesia for obstetrics and general surgery without the necessity of a special mattress or table has been proved successful at this hospital by using a simply constructed needle shield which will fit the back of any patient.

The needle shield, which makes continuous spinal anesthesia practical for the first and second stages of labor, with the patient in her own bed or on the delivery table, in any position desired, is simple in construction.

The shield, shown in Fig. 1, is bent to form from a sheet of galvanized iron, and measures 9 inches in length and $3\frac{1}{2}$ inches in width at the base. The flange which lies against the back is lined with a strip of felt. It is slightly curved in its entirety and measures 1 inch from the top of the felt lining to its greatest depth. The central portion of the base has a slightly indented area measuring $2\frac{1}{2}$ inches in diameter. The shield is designed for use with a malleable spinal needle.

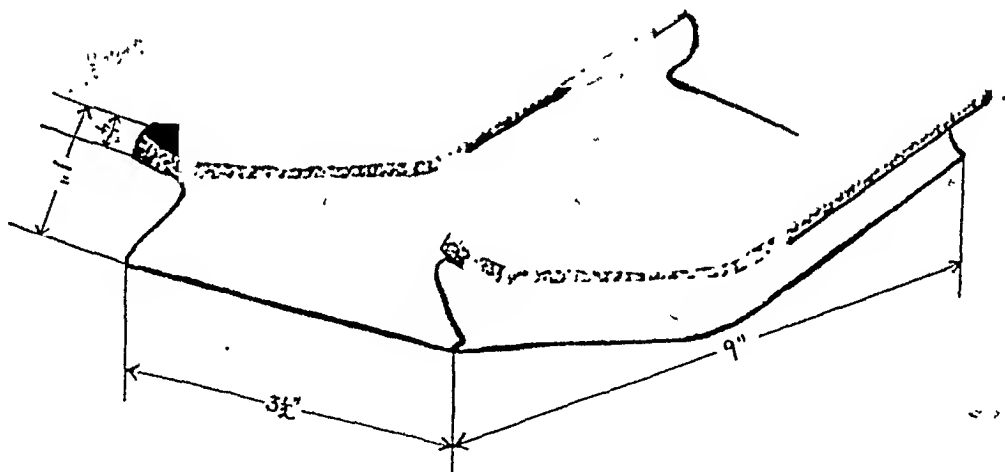


Fig. 1.

After making the spinal tap with a 19 gauge malleable spinal needle in either the sitting or lateral position, the stylet is removed and the regular continuous spinal rubber tubing of 2 c.c. capacity with a Luer-Lok connection is attached to the needle. The tubing, previously filled with anesthetic solution, has a one-way stopcock with a 10 c.c. Luer-Lok syringe attached to its opposite end.

The needle is then bent at right angles one-quarter to one-half inch away from the back and secured with adhesive tape. The needle shield is then placed over the needle and part of the tubing, and secured firmly to the back by placing adhesive tape along the undersurface of the felt-lined flange. The patient is then free to turn on her back or side at will, minus the imminence of dislodging the needle or the shield.

To permit the patient complete freedom of movement, the syringe may be detached from the tubing and a Luer-Lok metal tip from a broken syringe may be attached to the

*Now at the South Baltimore General Hospital, Baltimore, Md.

shutoff stopcock. This metal tip must have a drop of solder placed inside where the glass barrel formerly was so that it can keep the stopcock sterile and at the same time prevent any outflow of spinal fluid should the stopcock accidentally open.

Fig. 2 shows the needle shield under the patient with the rubber tubing supported against the body with adhesive tape. The sterility of the opening of the stopcock is maintained by the Luer-Lok syringe tip which is attached to the stopcock opening.



FIG. 2.

The shield was originally designed with the idea of applying Lemmon's continuous spinal technique to women in labor while lying in their own beds, but it has meanwhile proved eminently successful on any type of operating table without the use of a special split mattress for any type of surgery where continuous spinal anesthesia is desirable. Since the shield fits comfortably into the lumbosacral curve, it may offer some degree of support to this area when it is anesthetized. This is significant when it is realized that one of the contributing causes of postoperative backache after spinal anesthesia may be the complete relaxation of the muscles and ligaments of the unsupported, anesthetized area of the back.

The following observations gleaned from the work done at this hospital offer several suggestions:

1. The needle shield which was already described makes continuous spinal anesthesia for labor and delivery practicable for the first time.

2. With regard to the type of anesthetic solution used during labor and delivery, an extremely dilute solution produced sensory but almost no motor anesthesia of either the extremities or the uterus. Ten milligrams, or 1 c.c., of pontocaine solution was dissolved in 9 c.c. of 10 per cent glucose solution. At intervals of forty to sixty minutes, 2 or 3 c.c. were injected between the third and fourth interspace. Anesthesia carried to the height of the umbilicus produced little motor anesthesia, and, as a consequence, very little fall in blood pressure was encountered.

American Obstetric Services

THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY OF STANFORD UNIVERSITY SCHOOL OF MEDICINE

San Francisco, Calif.

THE origin of the Faculty of Medicine of the Stanford University is to be found in the establishment of a medical school in San Francisco in 1858 by a few medical gentlemen earnest in their desire for mutual improvement; anxious to increase their store of knowledge; and, like the true scientist the world over, ever willing, even eager, to import their knowledge to others.' They received a charter from the University of the Pacific, Santa Clara, and issued an announcement of lectures for the session of 1859. Dr. R. Beverly Cole was Professor of Obstetrics and Diseases of Women and Children, and Physiology. The announcement stated, "In this course there will be no lack of effort to bring everything pertaining to this department as clearly and practically before the mind of the student as the present state of the science will admit. The lectures will be amply illustrated by colored drawings, many of which have been taken from nature, and also by wet preparations. The different operations in obstetrics will be performed upon a manikin, and the student will be instructed and practiced in the use of obstetrical instruments."

In 1864 the young institution saw fit to suspend its teaching, the Toland School taking its place. The arrangement, however, proved an unhappy one, and in 1870 the men who had accepted professorships at Toland withdrew and reorganized the Medical Department of the University of the Pacific. Facilities for clinical instruction were obtained at the San Francisco City and County Hospital, and in 1871 Dr. Clinton Cushing became Professor of Obstetrics and Diseases of Children.

The following year further changes became necessary in order to obtain more adequate laboratory and classroom space. Relations with the University of the Pacific were severed, and the school became the Medical Department of University City College, although it was also known as the Medical College of the Pacific. That same year Dr. Henry Gibbons, Jr., who had graduated in 1863, became Dean as well as Professor of Obstetrics and Diseases of Women and Children, a post which he retained until 1912. A clear-cut separation of the two divisions of obstetrics and gynecology never occurred, but in 1881 a "special professorship" of gynecology was instituted and Dr. Clinton Cushing was given the chair. In 1899 the teaching assigned to this position was taken over by Dr. George B. Somers, first as lecturer and later as professor, while Dr. Cushing became emeritus in 1901.

The medical school had always been handicapped by the lack of a suitable building, and in 1882 the members of the faculty discussed the possibility of raising sufficient funds for this purpose among themselves. One of them, however, Dr. Levi Cooper Lane, endowed the school with a \$100,000 gift to construct an adequate building, and in 1890 he further contributed for an addition to the original structure. It was located on the corner of Sacramento and Webster Streets and although it has had many renovations in the course of the passing years, it is still the key building of the Stanford Medical School (Fig. 1).

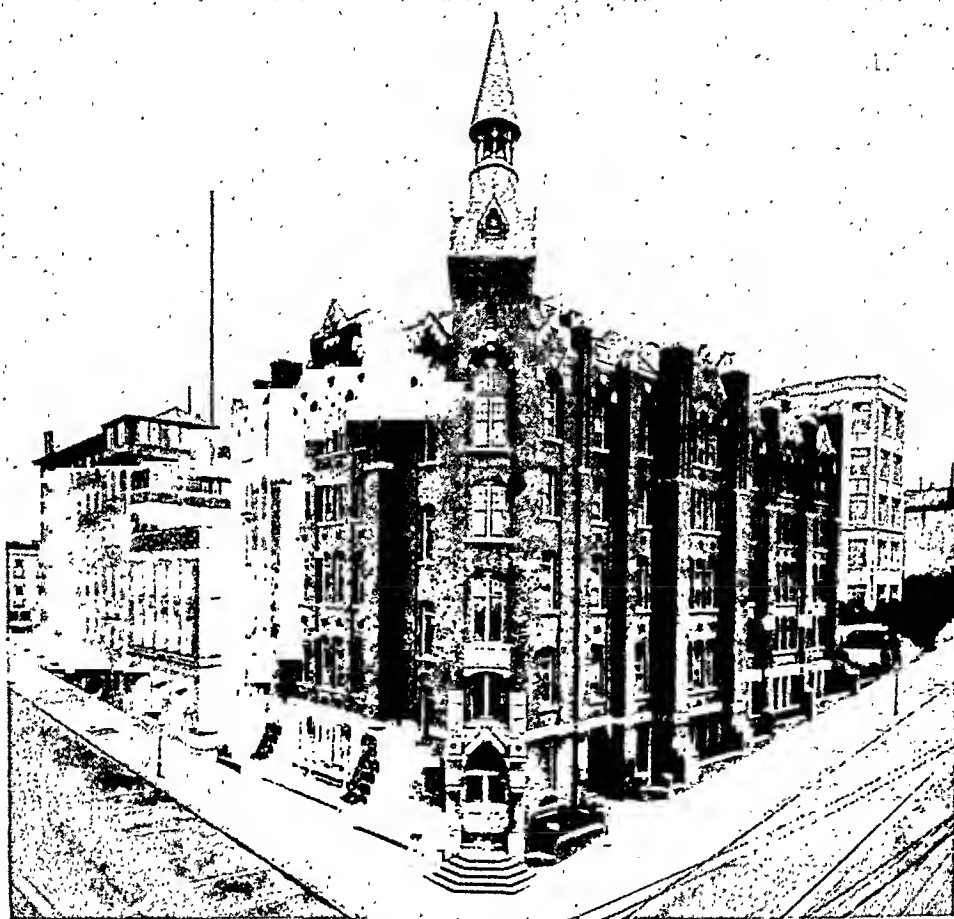


Fig. 1.—Stanford Medical School. To the left is Lane Hospital and the white building to the right is a wing of Stanford University Hospital.

With his first gift Dr. Lane made one condition, namely, that the building be given the name of his late uncle, Professor E. S. Cooper, a pioneer San Francisco physician who had founded the first medical school to function on the Pacific Coast. The faculty remained the same, but the institution from then on was known as the Cooper Medical College.

In those early days clinical facilities were provided by the 450-bed San Francisco Hospital and by the Morse Public Dispensary which had been established in 1870. The latter was maintained by the school for years but eventually was moved to the college building and became the Cooper College Dispensary. A notable advance occurred in 1894 when the generous benefactor of

the school donated a 100-bed hospital which was constructed adjoining the medical school building. The new building was rightly named "Lane Hospital" and is still the basic teaching hospital of the present institution.

In November, 1908, Cooper Medical College transferred its allegiance to the Leland Stanford Junior University. This entailed many changes, such as the construction of a new hospital and arrangements for some preliminary instruction for medical students at Palo Alto. In 1912 Dr. Alfred Baker Spalding assumed control as Professor of Obstetrics and Gynecology and his term of service saw the development of a well-organized department of obstetrics and gynecology and female urology devoted to the care of patients, teaching, and research. Because of ill-health Dr. Spalding was forced to retire prematurely in 1933, and was succeeded by Dr. Ludwig Augustus Emge, who did much to enhance the department's activities, and is now on active overseas duty with the United States Public Health Service.

Teaching Staff

The staff of the Department of Obstetrics and Gynecology is at the present made up almost exclusively of part-time teachers. There are two clinical professors, five associate clinical professors, five assistant clinical professors, one full-time instructor, seven clinical instructors, four assistants in instruction, and one research associate. Of this number six are on leaves of absence with one or the other of the Services of the United States.

Clinical and Laboratory Facilities

The department has clinical facilities at both the San Francisco City and County Hospital and the Stanford-Lane Hospital. These institutions are general hospitals, and at the San Francisco Hospital 18 beds are available for obstetric and 31 beds for gynecologic patients. At Stanford-Lane Hospital there are 15 beds for clinic and 19 for private obstetric patients, and 12 beds for clinic gynecologic patients. An additional 10 single-bed rooms are used for isolation and overflow of obstetric patients. Private gynecologic patients are cared for on the general wards of Stanford Hospital.

An Outpatient Department is associated with the medical school. Gynecologic patients are seen every morning and a prenatal clinic is held on two afternoons each week. In addition, special clinics are held on two mornings for female urology, one for postpartum examinations, two for endocrine problems, and a special Tumor Clinic is conducted on one morning.

In order to obtain a proper perspective of the number of patients attended by the department, it is important to note the great changes which wartime conditions have brought about. It has been especially marked in San Francisco, not only because of new economic standards, but because of a great increase in population due to the influx of men and women of the Service and workers in the various war industries. Since the majority of these newcomers belong to the younger age groups the changes are more marked on the obstetric service. In the period from September, 1937, to September, 1941, there were 1,662 de-

liveries on the Stanford-Lane Clinic service, and in 1941-1945 this number increased to 3,079. A similar change was observed on the private service, with 1,201 deliveries for 1937-1941, and 3,016 for 1941-1945. The gynecologic service likewise shows an increase, but not to the same degree. In 1937-1941 there were 1,362 hospital admissions as compared to 1,471 for the 1941-1945 period.

At the San Francisco Hospital a drop in the number of patients in both services also reflect the economic changes in the community. During 1937-1941 there were 1,393 deliveries and 2,924 admissions on the gynecologic service, as compared to 1,213 and 2,399, respectively, during 1941-1945.

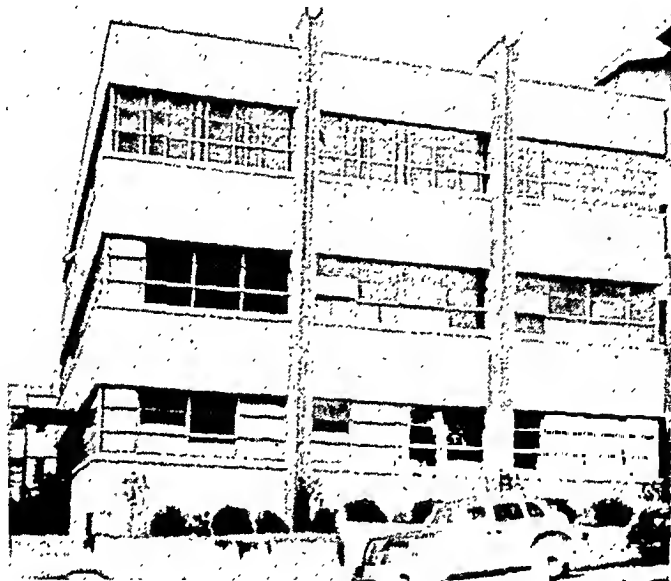


Fig. 2.—The Ruth Lucie Stern Research Laboratory.

In September, 1939, the Medical School acquired the Ruth Lucie Stern Research Laboratory (Fig. 2). It is a modern three-story building located across the street from Stanford Hospital, and a large amount of space was allocated to the Department of Obstetrics and Gynecology. On the first floor the Department has a large animal room and maintains both a rat and a mouse colony. There are also facilities for employing rabbits and frogs for pregnancy tests. Adjacent to the main room is a small animal operating room and a store-room. On the third floor of the building there are four administrative offices, a large room now used as a museum but which can be readily transformed into laboratory space or offices for assistants, a room for research workers, a large darkroom for photographic work, storage space, a chemical laboratory, and a pathologic laboratory. Since 1912 the Department has conducted its own examination of pathologic specimens obtained from the operating and delivery rooms. For instance, during the session 1944-1945, 1,282 specimens were studied and this has been an important feature of both undergraduate and graduate training.

A modern lying-in suite was built above one of the wings of Stanford Hospital and completed in the winter of 1942. Fig. 3 gives the floor plan and de-

tails may be found in the description given by Dr. Anthony J. J. Rourke.* Its main features are two waiting rooms for patients' relatives, four single-bed and one two-bed first stage rooms, a dressing room with sleeping accommodations for attending obstetricians, a small laboratory, sterilizing room, scrub room, and three delivery rooms. One of the latter is for teaching purposes. At one end is a students' gallery completely separated from the delivery room proper by plate glass. Students are able to enter this gallery without going through the unit. An amplifying system, with a microphone in the delivery room and a radio in the gallery, enables the obstetrician to talk to the students.

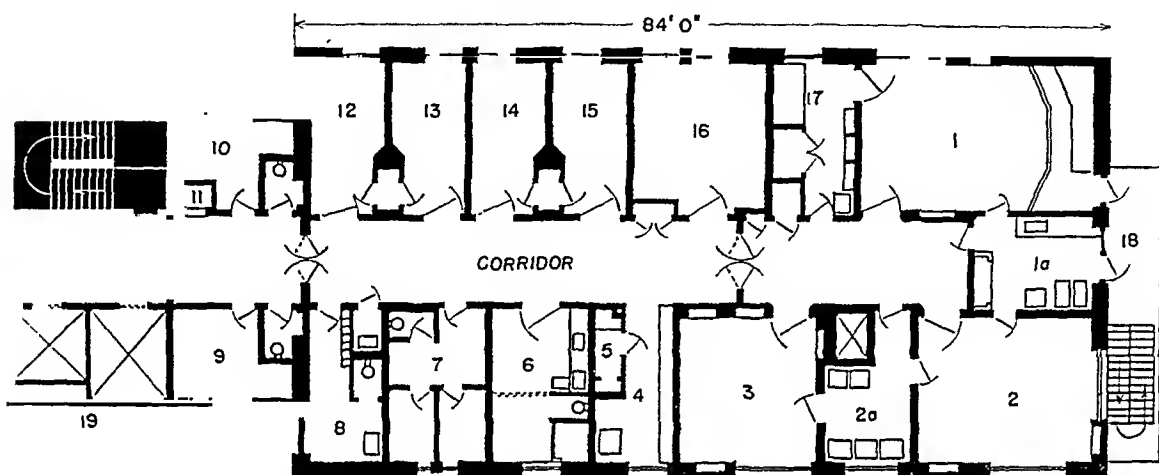


Fig. 3.—Stanford University Hospitals, Lying-in-suite (Jan. 31, 1942.)—Floor plan.

- 1, Delivery room and amphitheater.
- 1a, Sterilizing room.
- 2, Delivery room.
- 2a, Scrub room.
- 3, Delivery room.
- 4, Nurse's station.
- 5, Laboratory.
- 6, Preparation room.
- 7, Doctor's rest room.
- 8, Nurse's locker room.
- 9, Waiting room.

- 10, Waiting room.
- 11, Clothes chute.
- 12, Single-bed labor room.
- 13, Single-bed labor room.
- 14, Single-bed labor room.
- 15, Single-bed labor room.
- 16, Double-bed labor room.
- 17, Surgical supply room.
- 18, Amphitheater entrance.
- 19, Passenger elevators.

Graduate Training

The adoption of the 9-9-9 months' service as a wartime measure has necessarily entailed important modifications in the graduate training offered by the department, but before the war a definite plan was in vogue which made full use of the facilities of the two hospitals. At the San Francisco Hospital the interns are on a rotating service so that they spend a comparatively short time in obstetrics and gynecology, but a full-time assistant resident and a resident are assigned to the department, and at times their duties during the course of a year have been divided between the two hospitals. At Stanford-Lane the regular House Staff consisted of three interns, two assistant residents, and a resident.

During their first year the three interns rotated at specified intervals. They spent four months on obstetrics where they were responsible for the welfare of the clinic patients, with the assistance of two medical students, and under the supervision of the assistant residents. Another term was spent on the

*Modern Hospital 61: 56, 1943.

gynecologic service where they cared for patients admitted to the hospital and assisted at both clinic and private operations. The third period of four months was spent mostly in the outpatient department but entailed training in anesthesia, both in the operating and delivery rooms.

The two assistant residents divided their year between the two sections of the department. While on obstetrics they assisted at all the private deliveries and supervised the interns in the clinic. On their term of duty with the gynecologic service they acted as first assistants on both private and clinic patients.

In the third year of training (and sometimes during the second) the candidate for a future residency was encouraged to leave the department for a year's service in pathology, general medicine, or surgery. The fourth year found the trainee as Resident and given as much control of the clinical and laboratory facilities of the department as possible, but always under supervision. In later years, Dr. Emge made an innovation when a desirable resident was kept on the staff as a full-time instructor for an additional year, and this proved a very wise move both from the standpoint of the doctor concerned as well as of the department.

C. FREDERIC FLUHMANN, M.D.

Necrology

OLIVER PAUL HUMPTSTONE, prominent gynecologist and obstetrician of Brooklyn, New York, died at his home in Amsterdam, New York, on January 23, after a long illness, at the age of 70. After graduating from the College of Physicians and Surgeons of New York in 1899, he interned at the Methodist-Episcopal Hospital in Brooklyn, and steadily advanced until he became head of the department in 1915 and remained as such until his retirement a few years ago. Dr. Humpstone was also associated as consultant with several other hospitals and a prominent member of various local societies.

A competent and able clinician, an inspiring teacher, and an active practitioner for many years, Dr. Humpstone is to be credited with the development of the maternity service at the "Seneca," which has grown into an important activity in the Borough of Brooklyn.

Department of Reviews and Abstracts

Selected Abstracts

Placenta

Ware, H. Hudnall, Jr., Winn, W. C., and Schelin, E. C.: Premature Separation of the Placenta, *South. M. J.* 37: 163, 1944.

There were 175 cases of premature separation of the placenta in 13,441 deliveries at the Medical College of Virginia, an incidence of 1:73. Of this group 59 were severe. These were characterized by sudden onset with prompt disappearance of the fetal heart sounds quickly followed by maternal shock. It is thought that this type of separation probably begins near the center of placental attachment and therefore external bleeding may be scanty or delayed. The treatment for this type in 42.3 per cent was a cesarean section with or without hysterectomy, depending upon the degree of hemorrhagic infiltration into the myometrium. There were 116 mild cases. In this group 95.7 per cent had vaginal deliveries. Cesarean section in this group was reserved for those with pelvic dystocia, long undilated cervixes, or where it was imperative to control a profuse hemorrhage. Following delivery the uterus was packed in 9.4 per cent of the mild group and 33.8 per cent of the severe group. Transfusions were given in both groups when indicated.

The relationship of toxemia to premature separation is well established, occurring in 53.9 per cent of the severe group and 22.4 per cent of the mild group. External hemorrhage occurred in 91.5 per cent of the first group and 82.7 per cent of the latter group. History of trauma was obtained in 3.2 per cent of the entire series. Careful analysis of the case histories reveals that both the mild and severe group occurred more frequently in patients near term. However, the complication may be seen as early as the twenty-second week of pregnancy. Fifty-four per cent of the separations occurred during labor, and in 34 per cent the onset of labor occurred soon after the separation. Artificial induction of labor by the rupture of the membranes was performed in only 33 patients.

There was an uncorrected maternal mortality of 3.4 per cent. All deaths occurred in the severe group. It is worth noting that the mortality from vaginal deliveries was 14.7 per cent and in cesarean sections 4 per cent. Fetal mortality in the severe group was 91 per cent and in the mild group 46 per cent. Of the six patients who died, only one was delivered by cesarean section. This patient died with anuria on the second postoperative day and the autopsy revealed interstitial nephritis. Five patients died following vaginal delivery. Four of these died of hemorrhage despite uterine and vaginal packing. The fifth patient died within one hour after delivery without transfusion or packing. It is suggested that more massive transfusion followed by early hysterectomy may have salvaged some of these patients. Autopsy performed on two of the patients delivered vaginally showed extensive extravasation of blood in the myometrium.

WILLIAM BICKERS.

Pregnancy, Diagnosis, Physiology, etc.

Murray, John: Rh Antenatal Testing. A Suggested Nomenclature, *Lancet* 247: 594, 1944.

Murray describes a modified technique for Rh testing, using smaller test-tubes (2.0 by 0.2 inch), Wright and Colebrook throttled pipettes, and a multiple grooved slide.

After the series of 200 consecutive unselected antenatal mothers were ABO grouped, and found to be a representative sample of the populace, the author proposes a new nomen-

clature for describing the Rh groups. He names the cells after the sera with which they react and thus records the phenotype of cells in this manner: rh (Rh_4); Rh_1 (Rh_{13}); Rh_2 (Rh_{234}); Rh_1Rh_2 (Rh_{1234}); Rh_0 (Rh_{34}); Rh' (Rh_1); Rh'' (Rh_{24}); $Rh'Rh''$ (Rh_{124}); Rhy (Rh_{12}) and Rhz (Rh_{123}).

Murray contends that the antenatal Rh testing must do more than simply detect Rh-negative mothers, which is easily performed by the finger prick and only 2 sera; anti-Rh' (1 + 3) and anti-Rh'' (2 + 3) - with no test of patient's sera for antibodies. The more complete examination for genetic make-up and the presence of antibodies will ultimately be of valuable clinical assistance, as will an examination of the husband's cells when the mother is Rh_4 (Rh negative), to enable us to forecast possible genotypes of the unborn infants and the likelihood of incompatibility. (When a greater series of tests are performed, for statistically more accurate results, the author hopes to correlate these clinical and serologic findings.)

The author's Rh tests showed that 12.5 per cent of 200 unselected consecutive antenatal mothers were Rh negative and that 2 of the 25 Rh-negative had anti-Rh antibodies.

CLAIR E. FOLSOME.

Pregnancy, Complications, etc.

Browne, Francis J.: *The Significance of Signs and Symptoms in Toxaemia of Pregnancy*, Edinburgh M. J. 51: 449, 1944.

In the September, 1944, Honeyman Gillespie Lecture, delivered in the Royal Infirmary, Browne initiated his paper by recounting his results from posing three written questions to seven prominent and experienced London obstetricians. In each instance the experienced man was to answer each question without consulting anyone or any literature.

The questions bear repetition:

1. Does edema, either clinical or occult, always precede hypertension?
2. Does toxemic albuminuria ever precede hypertension?
3. Does toxemic albuminuria ever appear before edema?

Browne found the replies showed little agreement. With this introduction, the author then considers the triad of signs or symptoms, to see if he can arrive at a conclusion regarding their meaning or genesis.

In the consideration of edema the author reviews the theories of its genesis, the anti-diuretic hormone, hypoproteinemia, increased capillary permeability, increased venous and capillary permeability, and the role of the sex and other hormones. In the latter possible etiological theory, Browne states: "It is curious that but little attention has been paid to the hormones of the adrenal cortex." He reaffirms that edema is best controlled and even prevented by limiting the intake of common salt.

Browne summarizes the evidence, pointing hypothetically toward the unknown factors causing hypertension of pre-eclamptic toxemia. We can say (1) it is due to humoral, not a nervous mechanism; (2) it is not due to renal ischemia however produced; and (3) the pre-eclamptic candidate, after the third month of pregnancy, acquires a sensitivity to the action of pressor substances which is not due to any constitutional predisposition.

Albuminuria, the least important of the cardinal signs of pre-eclamptic toxemia in Browne's opinion, does not precede hypertension or edema. He regards the albuminuria as rather an effect than a cause and condemns the phrase "albuminuria of pregnancy."

Browne concludes that the antenatal clinic and care of the expectant mother furnish unparalleled opportunities for observation and investigation of the genesis and development of the toxemias of pregnancy.

CLAIR E. FOLSOME.

MacLennan, Hector R.: *Contracted Pelvis in Childbirth: A Study of Its Morbid Effects on Mother and Child* (The Blair-Bell Lecture, 1944), J. Obst. & Gynaec. Brit. Emp. 51: 293, 1944.

This Blair-Bell Memorial Lecture reviews a previous report regarding the geographical distribution of contracted pelvis in Scotland and analyzes the outcome of labor in a series of

1,049 cases from the standpoint of the toll of maternal and fetal life taken by contracted pelvises. Rickets is considered to be the chief etiological factor for major and minor degrees of contracted pelvises, and congenital or developmental morphologic variations are thought to be of secondary importance. This opinion was not gained by the use of roentgenologic methods of examination.

One of the striking features is the dystocia caused by slight degrees of contraction. There were 31 craniotomies and 53 high forceps operations. The stillbirth and neonatal death rates are high even though these cases were under the care of experienced obstetricians. The maternal death rate for the series was 21 per 1,000 (22 in 1,049). In the normal control group it was 3 per 1,000.

These results justify the importance of instituting adequate health measures to prevent the development of rickets in the growing child and the need for clinical and roentgenologic methods of examination for the early recognition of the abnormal pelvises. While the author believes it is extravagant and impractical to request a roentgenologic examination for every expectant mother, the value of roentgenologic methods is admitted. A roentgenologic examination with expert interpretation is advised for all primigravidas when the head has not engaged by the end of the thirty-sixth week. Multigravidas who have required instrumental deliveries should be regarded with suspicion, even when deliveries have been effected successfully, because increase in child weight may introduce hazards at any time with the slightly contracted pelvis. Hence the early recognition of the degree of pelvic contraction is urged in order to institute the proper treatment.

HOWARD C. MOLOY.

Puerperium

Palacios Costa, N., Pastorini, R., Jamarido, N., and Di Leo, A.: Vaginal pH During the Puerperium, *An. ateneo Inst. mat. y asist.*, 363-366, 1943.

The authors studied 54 women and found that those with a febrile puerperium had high pH values. The lowest pH was 4.7 and the highest 7.7, while the respective extreme temperatures were 36.2° and 38.8° C. This coincidence is an important finding, and further studies are needed to elucidate the reasons why the vaginal pH increases with the temperature of the body.

J. P. GREENHILL.

Abad, Ramon S., and Peiretti, Francisco S.: Permanent Enlargement of Pelvis After Symphysiotomy, *An. ateneo Inst. mat. y asist.*, 85-122, 1943.

The authors found this condition in 100 per cent of 35 women studied roentgenographically. The separation was not over 2 cm. in 57 per cent, and was about the same as that found by digital examination at the time of labor in 43 per cent.

One woman had a separation of 5 cm. due to a fall with the legs spread apart subsequent to the symphysiotomy; after disappearance of the pains and urinary disturbances resulting from the accident, there remained only an anterior and posterior colpocele which was successfully operated upon.

Another woman, who had two spontaneous deliveries since her symphysiotomy, presented a separation of 4.5 cm. when examined for a new pregnancy. This enlargement was greater than that obtained at the time of operation.

A separation of 3.5 cm., associated with difficulty in walking and pains in the sacral region, was reduced to 2.5 cm. with disappearance of the disturbances, by bed rest and a compressive bandage round the pelvis.

J. P. GREENHILL.

Radiation

Corscaden, James A.: An Evaluation of Radiation in the Treatment of Carcinoma of the Corpus Uteri, *J. A. M. A.* 126: 1134, 1944.

The author discusses the various methods that have been used in the treatment of carcinoma of the corpus uteri and some of the improvements in the more recent methods of

treatment. The use of hysterectomy alone or radiation alone or a combination of the two is discussed. All three methods are essential in operable carcinoma of the uterus. Hysterectomy alone promises only a 60 per cent five-year survival rate, and fails because of recurrences. The author's general conclusion is that x-rays have a definite cancerocidal effect and, while at present incompletely effective when used alone, should be considered as essential in the treatment of corpus carcinoma. Radium alone promises a five-year survival of 55 per cent, but, because of its local effect, fails to destroy cells lying deep in the myometrium and in metastasis in the adnexa. When a combination of these two methods is used, there has been a five-year survival rate of 70 per cent. It is felt that the employment of present-day techniques promises a five-year survival of 80 per cent.

WILLIAM BERMAN.

Sterility, Fertility, etc.

Grabill, Wilson H.: Effect of the War on the Birth Rate and Postwar Fertility Prospects, *Am. J. Sociol.* 50: 107, 1944.

A record of 3,100,000 babies were born in 1943. This will probably be reduced to 2,640,000 in 1944, and will continue to decline until the end of the war when a temporary peak will be followed by another decline. In the first World War, there was a rise during the first year which was soon arrested and a rapidly falling birth rate occurred during the latter years of World War I. The effects of World War I on birth rate continued until 1940. Military casualties and privations by civilian population contributed to this decline. A large factor, however, was the determination on the part of most people to limit family size. In the United States, birth rate tends to follow economic and political changes, although there has been an over-all decline in birth rate since the beginning of this century. The fluctuations have continued to parallel the rise and fall of economic conditions. The birth rate in this country has already passed its wartime peak and will continue to fall until the end of the war, reaching a low point of perhaps 16 births per thousand population. Immediately after the fall, a temporary revival is expected, but in the long run, the postwar trend will again be downward.

WILLIAM BICKERS.

Vaginal Infections

Compton, B. C., Bieren, R. E., Inloes, B. H., Kardash, Theodore, and Hundley, J. M.: Treatment of Gonococcic Vulvovaginitis, *J. A. M. A.* 127: 6, 1945.

The authors feel that the smear method of diagnosis is as successful as the culture method in children. This is not so true in adult gonococcic infections. The response to treatment can also be followed by the same method. The patient should be isolated in the home as completely as possible until the discharge has disappeared, and until the smear has become negative. The authors feel that estrogens are the drugs of choice. The sulfonamides have been used successfully both alone and in combination with estrogens. The authors abstain from the use of the sulfonamides because of the danger of sensitization of the patient to these drugs. They should be used for the more serious diseases occurring in childhood, and for some of the complications arising from gonococcic vaginitis. Patients are followed weekly until they have three negative smears, then at monthly intervals until they have been negative for three months, and then at three-month intervals thereafter until the smears have remained negative for one year. The technique of use of the various drugs mentioned is described.

WILLIAM BERMAN.

Fuenzalida, Sergio: Vaginal Trichomoniasis, *Bol. Soc. chilena de obst. y ginec.* 8: 393, 1943.

The author states that trichomonas is one of the most frequent causes of leucorrhea and has been found in 60 per cent of the patients with this disorder. The best way to discover the parasite is to examine fresh vaginal discharge mixed with 5 c.c. of physiologic salt solution. This must be done within two hours of collecting the discharge; otherwise,

the movements of the parasites decrease, making their recognition more difficult. The most common method of infection is by contact with the discharge of a parasite carrier. Venereal transmission is also possible. Symptoms appear or become worse whenever a change in vaginal pH toward alkalinity takes place.

Fuenzalida has obtained the best results with Devegan and silver picrate. In the first method, the vagina and vulva are irrigated with 1 liter of tincture of green soap and the discharge is removed by cautious use of cotton swabs. The soap is washed out with 1 liter of boiled water and the vagina is dried with cotton. Two tablets of Devegan are placed in the lateral cul-de-sacs. This procedure is repeated for three days and then three times more at intervals of four days. The patient places a tablet in the vagina every night for one month, with the exception of the days on which the treatment is given.

In the second method, the vagina is cleaned in the same manner and dried. Five grams of a 1 per cent mixture of silver picrate in kaolin are pulverized and placed in the vagina once a week for four weeks and the patient inserts into the vagina an ovule of silver picrate (0.13 Gm.) every night of the four weeks. With both methods, intercourse and irrigations are stopped for three months.

J. P. GREENHILL.

Venereal Diseases

Hughes, T. Dixon: Syphilis in Pregnant Women: A Study Based on the Routine Wassermann and Kahn Tests Performed on 28,924 Patients, *M. J. Australia* 2: 265, 1944.

The authors report 160 positive reactions for syphilis among 28,924 patients tested, which gives an incidence of 0.55 per cent. Of these 160 cases, only 134 records are available. One hundred and twenty children were born alive, 8 were stillborn, 4 died in the neonatal period, and there were two miscarriages. All of the above 134 patients had treatment, the adequacy depending upon how early in pregnancy they reported to the outpatient department. These figures lend support to the statement that syphilis contributes to fetal mortality in the last half of pregnancy.

WILLIAM BERMAN.

Rosenblatt, Philip, Meyer, Edda, and Robbins, Lillian: Statistical Studies in Female Gonorrhea With an Evaluation of Yeast Supplement in Gonococcus Isolation, *Am. J. Syph. Gonorr. & Ven. Dis.* 28: 634, 1944.

Conclusions reached are as follows:

1. Proteose No. 3 hemoglobin agar (Baeto) fortified with supplementary factors present in Baeto-Supplement A is superior to chocolate agar alone.
2. Cultures from the cervix uteri are more likely to be positive than cultures from the urethra.
3. The examination of smears for the diagnosis of gonorrhea in the female is unsatisfactory.

C. O. MALAND.

Marcano, G. M. O.: Influence of Nicolas-Favre Disease on Pregnancy, Parturition and Fetus, *Rev. obst. y ginec.* 3: 126, 1943.

The author discusses the above subject with a report of 17 cases. He says that because of the serious aspect that lymphogranuloma has assumed in Venezuela, the problem deserves special study. When pregnancy occurs, it will be carried to normal term in the majority of cases. Disturbances caused by the disease, however, can have serious repercussions on the fetus in some cases, and the mother is not free of risk. The amniotic fluid, in the latent period of the disease, lacks antigenic properties. Intrauterine infection does not occur in mothers who have chronic infection. They produce healthy infants, who develop normally. The Frey reaction is negative in children born of mothers with lymphogranuloma, at least in the latent period of the disease. Because dystocia is frequent with this disease, the patients should be subjected to vigilant observation during labor, and in serious cases cesarean section should be performed.

J. P. GREENHILL.

Malignancies

Aguinaga, A.: Cancer of Bartholin's Gland, *Obstet. y. ginec. latino-am.* 2: 178, 1944.

The author reports two cases of cancer of Bartholin's gland in women aged 46 and 66 years, respectively. Up to the present time, more than 60 cases of this type have been reported in the literature. Most women with cancer of Bartholin's gland were between 41 and 60 years of age, but cases occurred at 19 and 91 years of age. In most cases the chief symptoms are pain, tumor, and pruritus. According to Honan, four conditions must be fulfilled to diagnose a neoplasm of the vulva as of Bartholin-gland origin, namely: (1) typical vulvar localization, (2) deep penetration in the labium, (3) connection with the gland duct, and (4) presence of intact gland tissue. Schaffer added two more prerequisites, namely, it must be a true adenocarcinoma, and the skin must not be involved.

The prognosis is bad. Metastases appear early. Treatment consists of vulvectomy with one- or two-stage extirpation of the inguinocrural glands and postoperative radiation by roentgen rays.

J. P. GREENHILL.

Cesarean Section

Salzado, C.: Cesarean Section for Diaphragmatic Hernia, *An. brasil de ginec.* 9: 255, 1944.

The author reports a case of pregnancy in a woman who had a diaphragmatic hernia. At term he performed a cesarean section and sterilized the patient. Six years before becoming pregnant the patient had a lung abscess which healed, and one year before the gestation a phrenicectomy had been done on the left side. The diaphragmatic hernia was discovered when an x-ray plate was taken for gastrointestinal symptoms. Roentgen-ray examination showed that the upper part of the stomach rested within the thorax.

J. P. GREENHILL.

Endocrinology

Leatham, J. H., and Abarbanel, A. R.: Gonadotrophins and the Antihormone Problem, *West. J. Surg.* 52: 491, 1944.

The combination of human chorionic gonadotrophin with sheep anterior pituitary extract (Synapoidin) is capable of stimulating the human ovary. This product contains protein material which may produce protein reaction. "Antigonadotrophic" substances have been detected in the human being following the administration of equine gonadotrophin. The antagonists may be evoked by the hormone or by the protein material. Chorionic gonadotrophin is not antigenic; however, the sheep pituitary extract may be.

Six patients were injected with the combination of anterior pituitary extract and human chorionic gonadotrophin, and a study was made to determine whether antigonadotrophic substances were produced. Blood serum from these patients was injected along with 3 R.U. of synapoidin daily for three days into 22-day-old female mice. The weights of the ovaries and uteri were obtained after seventy-two hours, when the mice were killed. The average ovarian weight in the sera-synapoidin mice was 6.6 mg. as compared with the ovarian weight of 5.7 mg. in the mice injected with synapoidin alone. It was, therefore, concluded that no antigonadotrophic substance was present in the sera of patients treated with a combination of chorionic gonadotrophin with sheep anterior pituitary extract. WILLIAM BICKERS.

Simpson, Miriam F.: Gonadotropic Hormones With Special Reference to Their Action on the Female Reproductive Mechanism, *West. J. Surg.* 52: 287, 1944.

Cyclic ovarian phenomena and all dependent activity cease after hypophysectomy in the rat. The follicular apparatus undergoes atresia with the exception of the corpora lutea which, strangely, persist for long periods. All organs related to reproduction, the mammary glands, oviducts, uterus, and vagina, undergo regression. This regression can be reversed by im-

plantation of pituitary tissue as originally shown by Zondek and Smith. It was also shown that the urine of pregnancy contained a gonadotropin similar in its effect on the rat ovary to the pituitary extract itself. From the postmenopausal urine was extracted a gonadotropin which caused follicular growth but not rupture. These observations were apparent on the rat but to a considerably less extent on the primate. The discrepancy is explained on the basis that chorionic gonadotropin is a pituitary stimulant and not a direct stimulator of the ovary in the primate. Reaction of the rat ovary will vary depending on whether the injected hormone is derived from an extract of the pituitary gland (FSH, ICSH, LH) or derived from body fluids such as blood or the urine of pregnancy. Primates have proved extremely resistant to hormones; ovulation cannot be induced with doses successfully given to rats on a comparable weight basis.

WILLIAM BICKERS.

Lurie, L. A.: The Endocrine Factor in Homosexuality. Report of Treatment of 4 Cases With Androgen Hormone, *Am. J. M. Sc.* 208: 176, 1944.

Homosexuals have usually been divided into two broad groups—overt and latent. The overt homosexual, as the name implies, is one who has committed homosexual acts. The latent is one who has not as yet committed any homosexual act, but whose behavior can be explained only on the basis of repressed homosexual drives. Such individuals, as a rule, sooner or later resort to overt homosexual practices. A better classification, in the opinion of the author, and one that might avoid some of the criticisms directed at the purely psychoanalytic concept of homosexuality, is that of innate and acquired. The psychopathology of acquired homosexuality may be correctly explained on a psychoanalytic basis. The condition of the innate homosexual, on the other hand, can be best explained on the basis of a somatic factor in the form of an endocrine disorder.

Four cases of male homosexuality, varying in age from 13 to 22 years, are presented, all of whom fell into the "innate" group, manifesting secondary sex characteristics approaching the female type. In 3 of the cases hormonal studies showed evidence of an androgenic deficiency. All were behavior problems. Testosterone propionate was administered to each in 25 mg. doses triweekly over relatively long periods of time with striking results. Not only did such physical changes as growth of hair, deepening of the voice, masculine body configuration, etc., take place, but all evidence of homosexuality, emotional disturbances, and delinquencies cleared up as well. The importance of the endocrine factor is stressed, and a psychosomatic approach to the study of homosexuality is suggested.

FRANK SPIELMAN.

Gynecologic Operations

Zumel: Dangers of and Contraindications to Immediate Rising of Operated Patients, *Toko-ginec. pract.* 3: 153, 1944.

The author believes that gymnastics and early rising are useful for some but that immediate rising is inadvisable for most surgical patients. Early and immediate rising has been made possible by asepsis and local anesthesia. Immediate rising of an operated patient who does not have an arterial pressure close to normal is dangerous. Early and immediate rising is contraindicated in septic surgery of the large cavities.

J. P. GREENHILL.

Colmeiro Laforet, Carlos: Surgery of Senile Prolapse. Kahr's Operation, *Toko-ginec. pract.* 3: 268, 1944.

During 1943 the author performed this operation on five women whose ages ranged from 60 to 70 years. In all cases of prolapse in which he considers this operation necessary, he routinely gives an intramuscular injection of 10,000 units of estrogen every five days to improve the circulation of the genitalia which show senile involution. The injections are continued until fifteen days after the operation which in no case is performed before the prolapse has been reduced for at least two weeks.

The immediate results were generally good and the prolapsed part was efficiently supported in all cases. The subjective impression of the patients, on discharge was uniformly favorable.

The method deserves to be tried extensively. Its superiority over the other methods recommended for similar cases lies in its easy technique, slight operative trauma, and more favorable immediate and probably also late results in a high percentage of cases.

J. P. GREENHILL.

Erratum

In the article entitled "Cesarean Section Mortality," which appeared in the July, 1945, issue on page 41, I wrote "Waters states that most of their extraperitoneal sections are done for teaching purposes." Dr. Waters, in a personal communication, states that I misunderstood him. He had furnished the figures used in the article but they were not broken down. In the June, 1945, issue, Waters stated that of the 250 cases, 90 had pre-operative morbidity or sepsis, leaving 140 presumably clean cases. Correspondence and a personal discussion with Dr. Cosgrove have clarified the indications in the 250 cases, and an additional 233, a total of 483 Waters sections to July 1, 1944. The majority of the operations were performed in potentially or actually infected patients, whom we would have delivered vaginally (if necessary by craniotomy) or by cesarean-hysterectomy. There were 6 deaths, a rate of 1.24 per cent. Five were from infection. The low mortality demonstrates the increased safety of the Waters operation over that of the transperitoneal low cervical. Furthermore, vaginal delivery in patients with dystocia entails an increased mortality for both mother and fetus which has been little, if any, increased by the operation for the former, and certainly decreased for the latter.

WM. J. DIECKMANN, M.D., CHICAGO, ILL.

Item

American Board of Obstetrics and Gynecology, Inc.

The following diplomates have been certified and are added to the previously published list: Dr. Charles Barnard Cunningham, 401 S. First Street, Virginia, Minnesota; Dr. Joseph A. Gaetone, 108-19 70th Road, Forest Hills, Long Island, New York; Dr. Harry Hauptman, 240 Stockton Street, San Francisco, California.

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Original Communications

AN EVALUATION OF METHODS FOR THE TREATMENT OF URINARY INCONTINENCE*

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(From the Clinic of the Woman's Hospital)

OF ALL the patients who have been relieved of gynecologic symptoms, none are likely to bring more genuine satisfaction to a surgeon than those who have been cured of involuntary loss of urine. For patients who have this troublesome symptom, the discomfort of being wet is often increased by the unpleasant odor of decomposed urine and irritation of the tissues about the vagina, vulva, and thighs.

The degree to which women are disturbed by involuntary loss of urine varies. Some seem to adjust themselves fairly well to considerable leakage. Others complain bitterly of even occasional soiling of their clothing. The most pathetic patients are those who have had to endure constant leakage of urine, both day and night, for varying periods of time up to several years. Many have had the discouragement of one or more vaginal plastic operations that have failed to bring relief. It is not surprising that the inconvenience and physical discomfort of such an annoying condition results in depression and forces some of these women to regard themselves as social outcasts. To restore one of these unfortunates to a normal status in society by relieving her symptoms is always a surgical triumph.

Conditions which cause urinary incontinence are well known and may be summarized as follows:

1. Congenital anomalies of the urethra, bladder, and ureters, such as hypospadias, epispadias, extrophy of the bladder, and ectopic ureters which may terminate in the urethra, vestibule, vagina, or uterus.

*Read at a meeting of the Obstetrical Society of Boston, March 21, 1944, a meeting of the New York Obstetrical Society, Oct. 10, 1944, and a meeting of the Philadelphia Obstetrical Society, Nov. 9, 1944.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

2. Congenital anomalies or pathologic conditions affecting the function of the central nervous system. These include spina bifida, tabes, spinal cord pressure resulting from neoplasms, trauma to the vertebral column, and destruction of one or more vertebrae by tuberculosis.

3. Obstetric or surgical trauma to the urethra, bladder, or ureters, resulting in urinary fistulas or partial to complete loss of function of the urethral sphincter mechanism.

4. Tissue destruction from malignant neoplastic growths of the pelvic organs alone or in combination with irradiation therapy used to destroy such growths.

5. Lesions of the urinary tract, usually infectious in origin, such as urethritis, trigonitis, cystitis, and ureteral strictures. These conditions lead to frequency of urination, dysuria, and at times to partial loss of urinary control.

Out of this variety of conditions, two major causes are responsible for urinary incontinence in a high percentage of patients that come under treatment. They are obstetric or surgical trauma, and damage to tissues from malignant neoplasms either alone or in combination with irradiation therapy used to eradicate such growths. Incontinence of urine resulting from such injuries may be due to partial or complete loss of function of the sphincter mechanism which controls urination or to fistulous communications between the urethra, bladder, or ureters and the vagina or uterus.

It is the primary purpose of this presentation to record certain observations regarding the treatment of genitourinary fistulas and that troublesome condition of the urethra frequently referred to as "stress incontinence of urine."

Historical records prove that the nature and causes of urinary fistulas were understood long before surgical techniques had been devised for their closure. One of the earliest known cases of a vesicovaginal fistula is that reported by Professor Derry of the Faculty of Medicine of Cairo.⁸ His examination of the mummified body of Queen Henhenit one of the wives of Mentuhotep who reigned about 2050 B.C., revealed a contracted pelvis and a large vesicovaginal fistula. It is presumed that she died in childbirth at about 31 years of age.

Mahfouz⁸ gives credit to Avicenna, A.D. 1037, for having been the first to recognize fistulas as a cause for incontinence of urine in women following difficult labor and delivery. Kelly⁶ states that van Roonhuysen, 1663, was the first to "discover and put into execution a well-defined plan of operative treatment." His technique, as recorded, is interesting. With a patient in the lithotomy position, the fistula was exposed with a speculum. The margins of the fistula were denuded and brought into apposition with sharpened goose quills which were held in position by silk threads wrapped around their edges. The wound was dressed with flat wicks moistened with warm balsam oil and the vagina was filled with sponges saturated with the oil of sweet almonds.

Jobert deLamballe (1862) operated upon a large number of fistulas with considerable success and is probably the first to emphasize the importance of avoiding tension on the margins of a wound.⁹ It was his practice to place traction on the cervix with forceps and to close the denuded margins of a fistula with interrupted sutures. If it seemed necessary to relieve tension on the wound, he did not hesitate to incise the lateral vaginal walls or to detach the bladder from the uterus through a transverse incision in the anterior vaginal wall near the cervix.

Continued progress in the development of surgical techniques for closure of genital fistulas dates to about 1850. As stated by Kelly,⁶ "It remained for Gustav Simon (1854) of Darmstadt and for Sims (1852), Emmet (1855) and Bozeman (1856) in America to usher in a new era in the cure of genital fistulas and to lay the foundations of modern gynecology."

Contributions of other surgeons include:

1. "Flap splitting" as recommended by Colles² of Dublin in 1861 and between 1890 and 1891 by Martin, Trendelenburg, Sanger, Fritsch and others.
2. Free mobilization of the bladder and separate suturing of the bladder and vaginal walls as introduced by Mackenrodt in 1894.
3. Suprapubic extraperitoneal closure of vesicovaginal fistulas by Trendelenburg in 1881.⁵
4. Suprapubic transperitoneal operations for urinary fistulas by von Dittel in 1893.⁵

Use of these operative procedures has made it possible to close about 80 to 90 per cent of the genital fistulas which, until about 100 years ago, were considered practically incurable.

Operative techniques in use at present for closure of urinary fistulas are either the same as those devised by the pioneers in this field of surgery or are ones which invariably incorporate the principles laid down in the original techniques.

However, modern gynecologists have made significant contributions to the management of these patients and have developed many refinements in technique. They have come to realize that success or failure in wound healing depends nearly as much upon the general physical status of a patient as upon the condition of the tissues about the field of operation. The modern preparation of a patient for operation includes not only steps to eliminate urinary tract infections and to be certain that tissues about a fistula are free of inflammation but also measures to raise the general health of the patient to a good level. This may require rest, a high-protein, high-vitamin diet, and treatment of anemia by administration of iron, liver, and blood transfusions.

The gynecologist takes advantage of modern facilities for accurate localization of a fistula. The incidence of postoperative tissue necrosis and infections has been reduced by the newer methods of antisepsis, improvements in the quality of suture materials, and use of the sulfonamide drugs. A better understanding of the anatomy of the vagina has made it possible to carry out dissections in planes of cleavage that preserve the blood supply in layers of tissue that are used to close fistulas. Finally, ingenious vaginal plastic procedures have been devised and used with success to close large fistulas which, in the past, had been considered incurable.

All the original techniques for closure of a fistula utilized the same procedure, that is, denudation of its margins and closure with some form of interrupted suture material. Sims' contributions to this method included improved exposure of a fistula by placing a patient in a lateral prone position and use of the speculum which he devised. In this way he took advantage of atmospheric pressure to distend the vagina. Much of his success was also due to the use of silver wire sutures and certain instruments which he developed to insure exact placement and adjustment of these sutures. He also devised the block tin catheter for postoperative drainage of the bladder.

Success with the Sims method depends upon close adherence to certain details in technique, which include painstaking denudation of the margins of a fistula, complete excision of scar tissue, accurate placement of silver wire sutures

through the entire thickness of the vaginal and bladder walls down to the mucosa of the bladder, and careful adjustment of the sutures to insure perfect apposition of the denuded surfaces. Healing may fail if the tissues about the wound are under too much tension or if the tissues in the grasp of the sutures are too much constricted.

With modern surgical techniques and improvements in suture materials, some gynecologists consider the use of silver wire obsolete. It is true that wound healing can be expected with other types of suture material if the margins of a fistula can be carefully denuded and brought into apposition without tension. However, some members of the staff at the Woman's Hospital still believe that there is no equally reliable substitute for silver wire. When silver wire sutures are properly used the avoidance of tissue reaction is remarkable. It is useful in surgical techniques other than that described by Sims and has been used frequently with good results to close the vaginal wall after repairing an opening in the bladder with fine chromic catgut.

Personal experience with the Sims technique has brought the conviction that it is best suited for the closure of small to moderate-sized urethral and bladder fistulas which are reasonably accessible and those which are located on relatively flat surfaces. It is a difficult technique to apply to a fistula which is located near the lateral sulcus of the vagina or too close to the cervix. Other procedures are also more suitable for some of the fistulas which occur in the vaginal vault following complete hysterectomy or malignant neoplasms of the cervix. Obviously the Sims technique should not be used for any fistula unless it can be closed without undue tension on the surrounding tissues.

A study of our results suggests that wound healing following the Sims technique is not always as solid as that following other methods. In a few of our cases, scant leakage occurred soon after operation due to small areas, pinhole in size, which failed to heal. Some of these healed spontaneously. Others required subsequent operations. In a few cases, late recurrences, three months or longer after operation, necessitated further operative treatment to close small fistulous openings. It is possible that some of these failures were due to imperfections in surgical technique or to the fact that other procedures would have been more suitable in some cases where the original attempt by the Sims method failed to effect a cure.

For the closure of urethral and bladder fistulas, many surgeons now prefer plastic procedures which involve separation of the bladder and vaginal walls at the margins of a fistula and closure of a fistulous opening with two or more layers of tissue. Techniques described for this purpose are referred to as "flap splitting" and free mobilization of the bladder. "Flap splitting" was probably first recommended by Colles² of Dublin in 1861. He advised that the mucous membrane of the vagina be detached from the margins of a fistula and that the wall of the vagina be split into two layers of about equal thickness. One layer was left attached to the vaginal wall and the other to the wall of the bladder. The wound was then closed in two layers.

In 1894, Mackenrodt¹¹ recommended free mobilization of the bladder. This procedure required more extensive dissection but permitted closure of large fistulas with less tension on the surrounding tissues.

In all plastic procedures involving the anterior vaginal wall, including those for closure of fistulas, members of our staff have been impressed with the importance of separating the wall of the vagina from that of the bladder in the natural plane of cleavage. We believe that the original incision to open the vaginal wall should extend through its entire thickness and that further dissection to develop flaps should be carried out in a thin layer of loose areolar tissue, or so-called endopelvic fascia, which is always present in the space between the walls of the vagina and bladder. Dissection in this plane of cleavage is accompanied by a minimum of bleeding and disturbance of nutrition to the flaps because the vaginal wall is made up essentially of smooth muscle which is supplied by blood vessels and nerves distributed between its fibers. The wall cannot be split into layers without damage to its blood and nerve supply. For this reason we believe that solid healing of a fistula is more likely to occur if flaps, developed for its closure, are made up of the entire thickness of the vaginal wall.

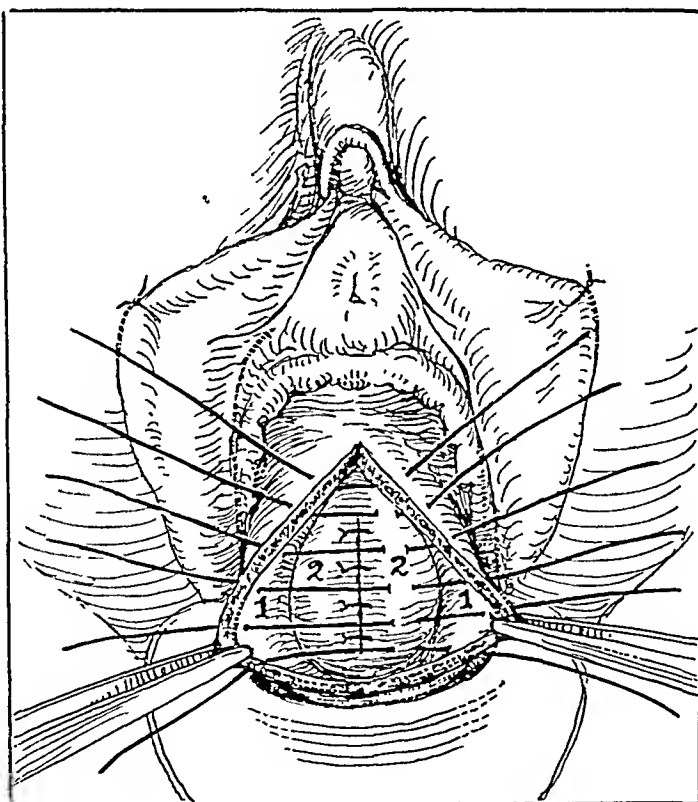


Fig. 1.

Technique

In Figs. 1, 2, and 3, steps in the closure of vesicovaginal fistulas following mobilization of the bladder are shown to emphasize certain points in technique.

Fig. 1 shows the closure of a midline fistula. Flaps of the vaginal wall, 1, composed of its entire thickness, have been separated from the bladder wall, 2, in the proper plane of

cleavage as previously described.¹ The fistulous opening in the bladder wall has been closed with interrupted sutures of fine chromic catgut. The placement of sutures for closure of the vaginal wall is also shown. It will be noted that in passing these sutures the bladder wall has been picked up at the left of the closed fistulous opening. When these sutures are tied, dead space will be eliminated and the suture lines in the vaginal and bladder walls will not be superimposed.

Fig. 2 shows a rather large vesicovaginal fistula. By free mobilization of the bladder it has been possible to close the original round opening in its wall with a wound which takes the shape of an inverted U. By this means tension on the sutures is reduced to a minimum.

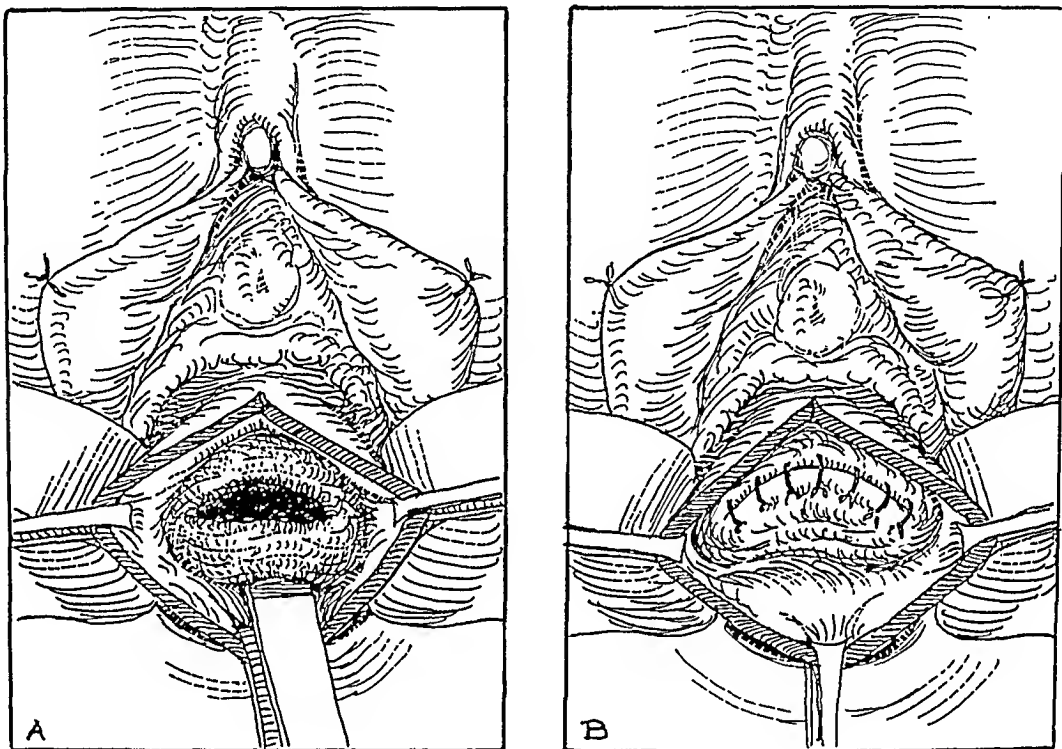


Fig. 2.

Fig. 3 shows three steps in the closure of a vesicovaginal fistula, using the Bissell modification of the Rawls "fascia lapping" technique for cystocele. In *A* the vaginal wall has been opened in the midline, well away from the fistula, to be certain of starting the dissection in the proper plane of cleavage. Subsequently the bladder wall is freely mobilized including the area about the fistula. In *B* the opening in the bladder wall is being closed with interrupted chromic catgut sutures. *C* shows how the right vaginal flap from which the mucous membrane has been denuded is drawn beneath the left flap with mattress sutures which have been tied. Also sutures have been placed to draw the left vaginal flap over the denuded surface on the right flap in order to complete the closure of the wound. By this method, openings in the vaginal and bladder walls are closed separately, and, finally, two well-nourished solid layers of tissue are placed over the closed fistulous opening in the bladder. This procedure has been successfully used for closure of some difficult bladder and urethral fistulas in which other methods have failed.

Results

A recent review of the records at the Woman's Hospital, from 1931 to date, revealed the fact that members of our staff had used some type of flap operation to close fistulas in about two out of every three cases that had come under treat-

ment during the past thirteen years. The more frequent use of these techniques has resulted from a better understanding of the anatomy of the vagina and the ability to develop satisfactory flaps for the closure of all types of urethral and

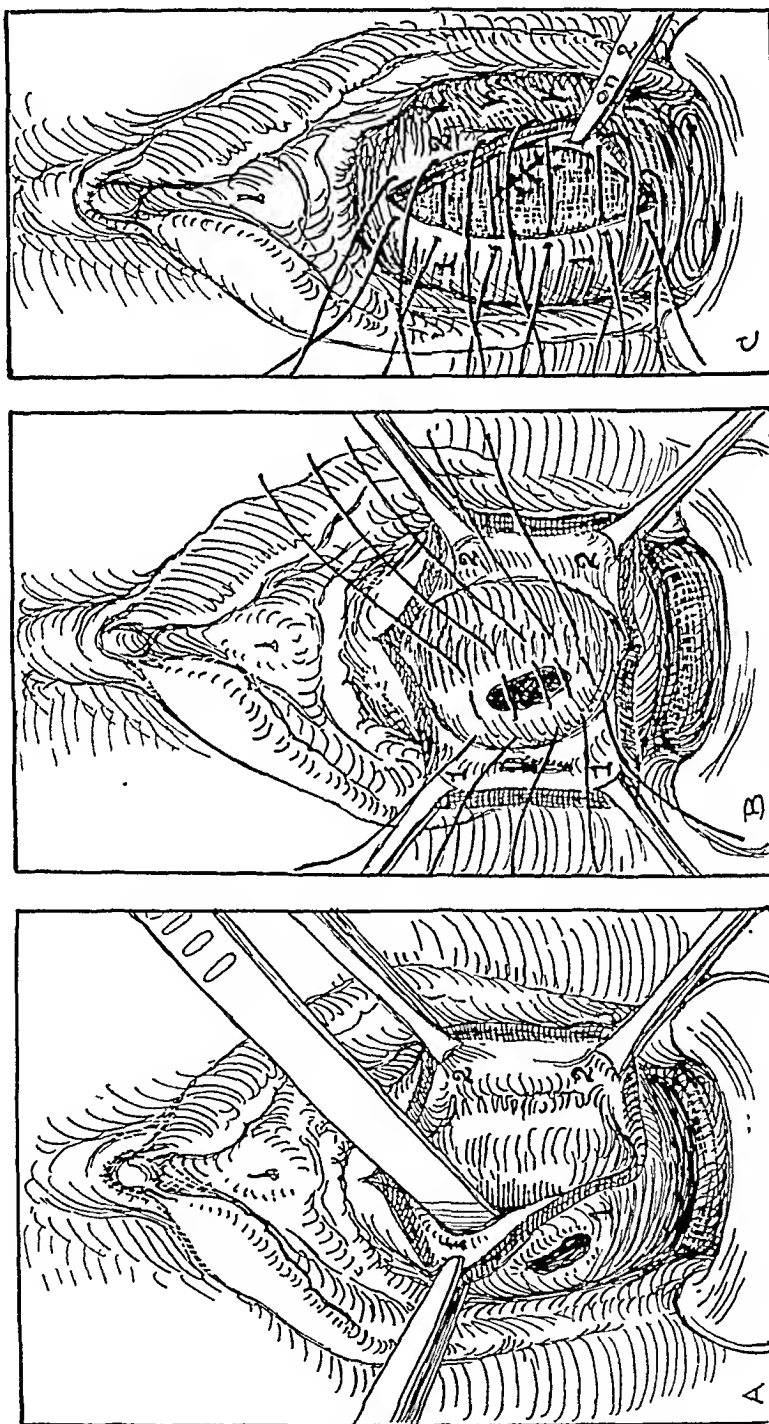


Fig. 3.

bladder fistulas. The success of the flap operations for fistulas which were difficult to close on account of their size or location has encouraged members of our staff to use these same techniques for many fistulas which, a few years ago, would have been treated by the classical Sims method. It seems possible that, in the future, closure of fistulas with well-nourished flaps, resulting from proper dis-

section of the anterior vaginal wall, may almost completely replace techniques which, for their success, depend upon closure of carefully prepared areas of denudation.

Although closure of fistulas by the transvesical route has been used with considerable success by some surgeons, experienced gynecologists will rarely find it necessary to resort to this method of approach. Visualization of fistulas which are difficult to expose can sometimes be facilitated by use of episiotomy or the Schuchardt incision, or by placing the patient in the Bozeman position.

An occasional fistula between the bladder or ureters and the uterus can best be treated by the transperitoneal route. Experience has proved that this method of approach involves the risk of serious infection to the peritoneal cavity.

In our experience, urethral fistulas are frequently difficult to cure. A great majority of these injuries are located at or near the junction of the urethra and bladder and are associated with damage to the urethral sphincter muscles. In this group must also be included the cases in which injuries have extended into the wall of the bladder or the urethra has been partially or completely destroyed.

An ordinary urethral fistula can usually be closed with the Sims method or with flaps developed about its margins. Treatment of injuries in this location requires a meticulous surgical technique. The flaps are usually thin and tissues must be approximated with great care to insure proper healing.

When destruction of tissue has been more extensive, so that the fistula involves the wall of the bladder or the urethra is partially or completely destroyed, it is usually necessary to resort to a plastic procedure to fill in the defect or to construct a new urethra. For this purpose various procedures previously described by Noble¹⁰ and Farrar⁴ have been used with success at the Woman's Hospital. These techniques utilize flaps developed from the anterior vaginal wall or labia minora. More than one operation may be required to repair such injuries.

From a study of our records it seems obvious that some operations to close urethral fistulas or to construct a new urethra may have failed as a result of unsuitable postoperative drainage of the bladder. In recent years, some members of our staff have resorted to more frequent use of suprapubic drainage. They are convinced that better operative results can be obtained and that some failures can be prevented if the trauma of an indwelling urethral catheter or frequent catheterizations is avoided.

If there is reason to believe that function of the sphincter muscles has been impaired in any patient who has a urethral fistula, steps should be taken to repair this injury as well as to close the fistulous opening. From a patient's standpoint, closure of such a fistula accomplishes little unless function of the sphincter muscles can be restored.

The procedures that are available for this purpose are the same as those which are used for relief of so-called "stress incontinence of urine." The most widely used surgical technique is that devised by Kelly as shown in Fig. 4.

By this procedure the urethra is first dissected free from the overlying vaginal wall. With a mushroom catheter in the urethral canal, the damaged and

overstretched internal sphincter muscle of the urethra is located and repaired with one or more mattress sutures of silk or linen. Before closing the incised vaginal wall an effort is made to reconstruct a proper support for the urethra from the surrounding tissues by use of fine chromic catgut sutures.

Through follow-up studies gynecologists have come to realize that the possibility of completely relieving stress incontinence of urine by surgical means is always uncertain. This has led to studies aimed at a better understanding of factors responsible for its occurrence and to more extensive plastic procedures for its correction.

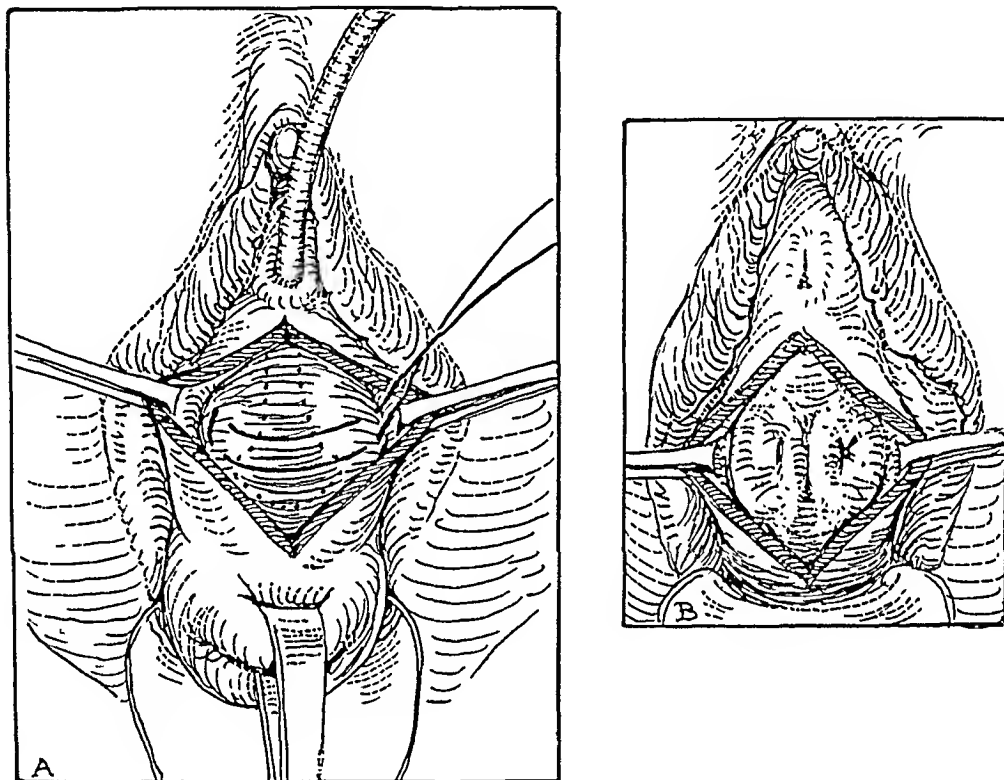


Fig. 4.

Kennedy⁷ believes that in some cases control of urine is prevented by scar tissue which fixes or distorts the normally circular sphincter muscles of the urethra at some point. In such circumstances, he believes that these muscles when contracted take the form of an ellipse rather than a circle and that proper compression of the urethra fails to occur. An important feature of the operation which he has developed includes free mobilization of the urethra on either side to be certain that it is not left fixed by scar tissue to either ramus of the pubis.

Davies³ believes that the location and functions of the levator ani, deep transversus perinei, and bulbocavernosus muscles are such that they should be regarded as voluntary sphincter muscles of the urethra.

The truth of the matter is that we do not yet have a clear understanding of the anatomy and physiology of the urethra or of the sphincter mechanism which controls urination. However, the technique of all plastic operations developed for the treatment of this condition are aimed at the accomplishment of objectives which are believed to be important. These are a restoration of the caliber of the over-stretched urethra to a size that is recognized as normal, repair of the

damaged sphincter muscles, replacement of the urethra to a normal position beneath the pubic arch, and reconstruction of a proper support for the urethra from the surrounding tissues.

Some patients who have had one or more operations for stress incontinence will have urethras which seem normal as to caliber, position, and appearance, and yet they are still incontinent. Some of these patients have had the benefit of expert gynecologic care. Extensive destruction of the urethral sphincter muscles may be responsible for some of these failures. Furthermore, it seems quite possible that lack of success in other cases may be due to damage to nerves which supply these muscles. Most gynecologists will admit that 10 to 20 per cent of patients with urinary stress incontinence are not cured by vaginal plastic procedures. In the past some of these patients have been advised not to submit to any further operative treatment.

About three years ago, the author decided to combine a vaginal plastic operation with transplantation of abdominal fascia with the hope of curing a patient who was 51 years of age and had been incontinent for twenty-nine years although she had had three previous unsuccessful vaginal plastic operations for the same complaint. A report on this patient's history and a description of the operative technique that was used have been published.¹ It is satisfactory to be able to report that after more than three years after operation this patient is still continent and free of any urinary tract symptoms. In the meantime, five additional patients have been operated upon by the same technique. One of these patients is still in the hospital and it is too soon to know the result of her operation. Histories of the other four patients may be briefly summarized as follows:

CASE 1.—Mrs. R. W., No. 78792, aged 38 years. Three normal pregnancies. Two spontaneous and one forceps delivery. About one year prior to admission, she had had a fibroid removed from the anterior vaginal wall. Urinary incontinence began following this operation and was not relieved by a second operation four months later for a vesicovaginal fistula which developed following the first operation. On Oct. 16, 1942, about one year after the original operation for fibroid, a combined vaginal plastic and transplantation of abdominal fascia was done for urinary incontinence due to a very much relaxed urethra. Dissection on the right side of the vagina was extremely difficult as a result of scar from two previous operations. Thirteen days after this operation, the patient again leaked urine from a small vesicovaginal fistula due to tissue slough in the same area where she had previously had a fistula. Obviously, the fascial sling was not disturbed because the patient has been continent and free of symptoms since closure of the recurrent fistula two years ago.

CASE 2.—Mrs. G. T., No. 77915, aged 48 years. Incontinence of urine followed two normal pregnancies and spontaneous deliveries. Past history revealed nothing remarkable except a diagnostic curettage and insertion of radium for hyperplasia of the endometrium seven months prior to the admission for repair of her birth injuries. Examination revealed a marked relaxation of the urethra, a moderate cystocele, a moderate rectocele, and a second-degree laceration of the pelvic floor. At operation on Feb. 15, 1943, all birth injuries were repaired and the relaxed urethra was treated with a combined vaginal plastic and transplantation of abdominal fascia. The patient had a postoperative urinary tract infection which subsided. She has been continent from the time of operation twenty months ago.

Comment.—The combined vaginal and abdominal technique was used because of marked relaxation of the urethra and the uncertainty of relief with only a vaginal plastic procedure.

CASE 3.—Mrs. L. J., No. 71952, aged 40 years. History of four pregnancies which resulted in three spontaneous abortions, two at four months and one at six months, and one full-term spontaneous delivery. At 27 years of age, she had a right oophorectomy and a vaginal plastic for birth injuries. From examination it appeared that the cervix had been amputated and that the uterus had been interposed. Soon after operation she developed a temperature of 106° F. Sutures were removed from the vaginal wall for drainage and the wound was allowed to heal by granulation tissue. Urinary incontinence, which was nearly complete, dated to this operation and was obviously due to a very much relaxed urethra.

On April 22, 1940, a vaginal plastic operation by the Kennedy technique was done. Although the result of the operation appeared to be good and the incontinence was somewhat improved, leakage of urine continued.

On Feb. 7, 1941, ten months later, a second attempt to relieve the incontinence by the Kennedy vaginal plastic technique failed to effect a cure.

On April 20, 1943, fourteen months after the second operation, a combined vaginal plastic and transplantation of abdominal fascia was done. This patient's convalescence was complicated by various psychoneurotic manifestations which made it difficult to evaluate the result of her gynecologic treatment. She was finally convinced that the result was satisfactory and now at thirty months after operation, she is continent and free of any urinary tract symptoms.

CASE 4.—Mrs. A. T., No. 50394, aged 39 years, Italian, height 4 feet 8 inches, weight 163 pounds. The patient had had fifteen full-term pregnancies, one premature labor at 7½ months, one spontaneous abortion at 3 months. In 1932, at the Woman's Hospital, she had had an operation for lacerated pelvic floor, cystocele, rectocele, lacerated eroded cervix, retroversion and partial prolapse of the uterus, and stress incontinence of urine, which was followed by a marked postoperative urinary tract infection. The final result was good except that some leakage of urine continued. In 1934, two years later, she had a second operation in another hospital for incontinence of urine with relief for three months, when leakage recurred.

In February, 1942, an attempt was made to relieve the stress incontinence by a combined vaginal plastic and transplantation of abdominal fascia. The operation was technically difficult on account of obesity. Fascial strips were obtained through a low transverse incision beneath a large pendulous abdomen. The postoperative course was complicated by a moderate wound infection and a recurrence of the urinary tract infection which has never been entirely eliminated. She has been treated off and on in our urologic clinic during the two years and nine months since her last operation. When the bladder irritation is controlled, she is continent for considerable periods of time. Although I hesitate to report this patient as cured of incontinence, it does seem that the operative result, from the mechanical standpoint, is satisfactory. This case demonstrates the difficulties which may be encountered in attempting to relieve incontinence in any patient who has a chronic urinary tract infection.

Including a case previously reported, four patients with persistent stress incontinence have been cured by vaginal plastic operations combined with transplantation of abdominal fascia. The fifth case is probably a success from the mechanical standpoint and may be cured if and when the urinary tract infection is eliminated. In addition to these five cases, Studdiford¹³ has reported four cases, and Holden¹³ one case operated upon by this same technique without failures. In other words, the results in nine out of ten cases operated upon by three gynecologists have been successful.

Eventually it is hoped that this technique can be used to establish urinary control in patients, in whom it is necessary to reconstruct a urethra which has been partially or completely destroyed and in those in whom the sphincter muscles are incompetent as a result of congenital defects in development.

Tables I to V, inclusive, give a summary of data regarding 118 patients who came under treatment at the Woman's Hospital for urinary fistulas from 1931 to date.

Table I shows the number and types of fistulas which were treated and the etiological factors which were responsible for their occurrence.

TABLE I. SUMMARY OF 118 URINARY FISTULAS AS TO ETIOLOGY AND TYPE

ETIOLOGY	NO.	TYPE OF FISTULA							TOTAL	PER CENT
		VESICO-		URETHRO-		URETERO-				
		VAG.	CERV.	VAG.	VES- ICO- VAG.	VAG.	CERV.	ABD.		
OBSTETRIC TRAUMA	37	28		3	6				37	31.4
POSTOPERATIVE									62	52.5
<i>Hysterectomy</i>										
Supravaginal	2	1					1			
Complete, abdominal	29	21				8				
Complete, vaginal	2	1				1				
<i>Myomectomy by va- gina</i>	1					1				
<i>Vaginal plastic opera- tion</i>	19	6		10	2	1				
<i>Miscellaneous</i>										
Ovarian cysts, intra- ligamentous	2							2		
Resection of infect- ed anomalous ureter	1						1			
Radium for benign uterine bleeding	1			1						
<i>Caesarean Section</i>										
Cervical (low flap)	1		1							
Extraperitoneal (Latzko)	2					2				
Porro	2	1					1			
TUBERCULOSIS									1	0.8
Spontaneous perfora- tion of bladder ulcer to vagina	1	1								
CARCINOMA									18	15.3
<i>Cervix Uteri</i>										
No treatment	2	2								
Irradiation	11	11								
<i>Corpus Uteri</i>										
Irradiation and com- plete hysterec- tomy	4	3				1				
<i>Ovary (2 operations)</i>	1						1			
TOTAL	118	75	1	14	8	14	4	2	118	100.0

It is interesting to note that approximately one-third (31.4 per cent) of these fistulas were due to obstetric trauma, that about one-half (52.5 per cent) followed various types of operations on the pelvic organs, and that 15.3 per cent were caused by malignaney of the pelvic organs either alone or in combination with irradiation therapy. These statistics confirm the observations of other authors on this same subject, namely, that the incidence of postpartum fistulas has been markedly reduced by modern obstetrie methods and that extensive pelvic operations in use at present are responsible for a considerable increase in the incidence of postoperative urinary fistulas.

Before using irradiation therapy for the treatment of malignaney of the

TABLE II. SUMMARY OF TREATMENT OF 118 URINARY FISTULAS

TYPE OF FISTULA	NO.	OPERATION						RESULT OF TREATMENT					
		NONE	SIMS	FLAP	IMPLANT OF URETERS TO		Neph-rectomy	OTHER	PALLIATIVE		OPERATIVE		
					BLADDER	BOWEL			UN-CHANGED	SPON. HEALING	CURED	IM-PROVED	FAILED
Vesicovaginal	75	18	23	32		1		1*	15	3	48		7
Urethrovaginal	14	4		9				1†	4		8	1	
Urethrovesicovaginal	8	1		5		1		1‡	1		3	2	1
Vesicocervical	1							1§			1		
Ureterovaginal	14	6			7		2		1	5	8		1
Ureterocervical	4				1		2				3		
Ureteroabdominal	2			1	1		1				2		
TOTAL	118	29	23	46	9	2	5	4	21	8	73	3	8

*Transvesical closure of fistula.

†Reconstruction of urethra—Farrar technique.

‡LaForte operation using rectocele to close opening in urethra and bladder. Martins technique for incontinence.

§Complete hysterectomy. Repair of fistula by transperitoneal route.

pelvic organs, it is our practice to examine the urinary tract of every patient. Although these examinations help to determine the extent of the disease, it is frequently difficult or impossible to know whether a urinary fistula which occurs following treatment is due to destruction of tissue by cancer or irradiation therapy or both.

The greatest number of postoperative fistulas occurred following complete abdominal hysterectomy. A few of these were due to accidents at time of operation. However, in most of these cases, leakage of urine began about two weeks after operation and were probably due to infection and trophic disturbances in the tissues about the vaginal vault and bladder.

Of the 19 fistulas following vaginal plastic operations, some were obviously due to imperfections in surgical techniques. Others occurred in cases where tissues were poorly nourished and dissections were difficult on account of scars from extensive birth injuries or from one or more previous plastic procedures for the same conditions.

In Table II management of the 118 patients who had urinary fistula is summarized.

Of the 118 patients, 29 had palliative treatment only and 89 had one or more operations as follows:

<i>No. of Patients</i>	<i>No. of Operations per Patient</i>	<i>Total</i>
73	1	73
4	2	8
11	3	33
1	4	4
<u>89</u>		<u>118</u>

In cases that were operated upon more than once, only the result of the final operation is recorded in Table II.

It will be noted that three vesicovaginal and five ureterovaginal fistulas healed spontaneously. Seventy-three of the 89 patients treated by surgical means were cured, 3 were improved, 8 had failures, and 5 died. Eighty-one, or 76.2 per cent, of the 118 patients were cured by palliative or surgical means. Of the 89 patients operated upon, 73, or 82 per cent, were cured.

The actual number of operations by various techniques used to close 89 fistulas treated by surgical means is summarized in Table III.

TABLE III. SUMMARY OF 118 OPERATIONS USED FOR CLOSURE OF 89 URINARY FISTULAS

OPERATION	NO.
Classical Sims	30
Flap	65
Implantation of ureters to:	
Bladder	9
Bowel	2
Nephrectomy	5
Transvesical closure of fistula	1
Transperitoneal closure of fistula	1
LaForte operation using rectocele to close a urethro-vesico-vaginal fistula	1
Reconstruction of urethra (Farrar technique)	2
Reconstruction of urethra with labia minora	2
TOTAL	118

TABLE IV. OUTCOME OF PALLIATIVE TREATMENT OF 29 URINARY FISTULAS

REASON FOR NO OPERATION	TYPE OF FISTULA				OUTCOME	
	VESICO-VAGINAL	URETHRO-VAGINAL	URETHRO-VESICO-VAGINAL	URETERO-VAGINAL	HEALED	UN-CHANGED
Spontaneous healing	3			5	8	
No incontinence		2				2
<i>Operation inadvisable</i>						
Contracted bladder and dilated ureters	1					1
No function one kidney and dilated ureters	1					1
Advanced carcinoma of cervix and vagina	10					10
Tuberculosis of bladder	1					1
Diabetes—psychopathic		1				1
<i>Considered inoperable</i>						
Extensive destruction of tissue	1		1			2
Refused operation	1	1				2
No follow-up				1		1
TOTAL	18	4	1	6	8	21

In Table IV the outcome of palliative treatment of 29 patients with urinary fistulas is recorded.

This table shows that eight of the 29 fistulas healed spontaneously. In 10 of the 29 cases in this series, fistulas followed irradiation therapy for carcinoma of the uterus. Experience has proved that such fistulas are difficult to cure.

Table V is a summary of data regarding the treatment of 11 patients in whom surgical treatment failed or was only partially successful in relieving symptoms.

The three factors which were responsible for unsatisfactory results in the 11 cases were extensive destruction of tissue, excessive scar formation as a result of the original injuries or previous plastic operations, and devitalization of tissue following irradiation therapy for uterine carcinoma.

Table VI is a summary of the five deaths that occurred following surgical treatment of the 89 urinary fistulas. If the sulfonamide drugs or penicillin had been available at the time that these patients were operated upon, perhaps some of the deaths could have been prevented.

Summary

To summarize it may be stated that:

1. Urinary incontinence may be due to fistulous communications between the urethra, bladder, or ureters and the vagina or uterus. However, the most frequent cause for loss of urinary control is incompetence of the urethral sphincter mechanism which controls urination.

2. In the series of 118 urinary fistulas that has been reported, approximately one-third were caused by obstetric trauma, about one-half by surgical trauma, and 15 per cent by malignant neoplasms of the uterus, alone or in combination with irradiation therapy used in treating such tumors.

3. Success in the treatment of a urinary fistula will depend upon careful preparation of a patient for operation, accurate localization of the fistula, and selection of a technique best suited to conditions found before and at time of operation.

4. Repair of a fistula by a technique which depends upon denudation of its margins should never be attempted unless closure can be accomplished without undue tension on the surrounding tissues.

TABLE V. DATA REGARDING PARTIAL AND COMPLETE FAILURES AFTER 11 OPERATIONS FOR URINARY FISTULAS

TYPE OF FISTULA	NO. OF OPERATIONS		OPERATIONS	RESULT	PROBABLE REASON FOR POOR RESULT
	OTHER HOSPITALS	WOMAN'S HOSPITAL	WOMAN'S HOSPITAL		
Vesico-vaginal	0	1	Schuchardt incision, Sims	Failed	<i>Devitalized tissue.</i> Fistula followed radium and hysterectomy for carcinoma of corpus uteri
	2	1	Flap (Bissell) overlapping	Failed	<i>Scar from previous operations. Extensive tissue destruction.</i> Fistula 5 cm. in diameter. Urethra detached from bladder
	1	1	Flap	Failed	<i>Scar from previous operations.</i> Followed vaginal hysterectomy. Healed but recurred after 3 months
	0	1	Transvesical closure	Failed	<i>Devitalized tissue.</i> Fistula followed irradiation for carcinoma of cervix. Schmitz III. L. of N. II. Closure impossible by vagina
	0	1	Schuchardt incision, flap	Failed	<i>Devitalized tissue.</i> Fistula followed irradiation and hysterectomy for adenocarcinoma of corpus uteri with extension to cervix
	0	3	1. Schuchardt incision, flap 2. Flap 3. Flap	Failed	<i>Extensive tissue destruction.</i> Fistula 5 cm. in diameter. Extended from urethra to cervix. Much improved by operations
	5	3	1. Flap 2. Flap 3. Flap	Failed	<i>Extensive tissue destruction and scar tissue.</i> Fistula followed pubiotomy. Urethra displaced posteriorly near right ramus of pubis
Urethro-vesico-vaginal	8	3	1. Flap 2. Plastic (Farrar) 3. LaForte-rectocele used to close defect	Failed	Extensive tissue destruction and scar tissue. No urethra. Tissue in poor condition. Obesity (280 lb.)
Urethro-vaginal	0	1	Plastic (Farrar)	Improved	Fistula followed vaginal plastic. Urethra almost completely destroyed. Continent for 3 hours after Farrar plastic
Urethro-vesico-vaginal	2	1	Flap (Bissell)	Improved	<i>Extensive scar from previous operations.</i> Fair result from operation. Continent for 2 to 3 hours
	5	3	1. Flap (Bissell) 2. Flap 3. Plastic (labia minora)	Improved	<i>Extensive destruction of tissue and scar tissue.</i> Urethra destroyed. Fistula in bladder 2 cm. in diameter. Could hold urine for 2 to 3 hours

5. Flaps developed for closure of a fistula should be made up of the entire thickness of the vaginal wall to insure optimum nerve and blood supply.

6. The importance of closing a fistula with the first attempt is obvious. Every surgical failure decreases the chance for ultimate success.

7. Vaginal plastic procedures are successful in curing about 80 to 90 per cent of patients who have urinary incontinence due to relaxation or partial destruction of the urethral sphincter muscles.

TABLE VI. MORTALITY RESULTING FROM OPERATIVE TREATMENT OF 89 URINARY FISTULAS

TYPE OF FISTULA	AGE	ETIOLOGY	OPERATION	CAUSE OF DEATH
Vesicovaginal	37	Obstetric trauma	Sims	Bacteremia
Urethrovaginal	52	Postoperative vaginal plastic	Flap	Pulmonary embolism
Vesicovaginal	55	Carcinoma corpus uteri. Radium and complete hysterectomy	Implantation ureters to bowel	Pulmonary embolism Septicemia and pulmonary embolism
Urethrovaginal	50	Postoperative vaginal plastic	Implantation ureters to bowel	
Ureterovaginal	40	Postoperative complete hysterectomy	Implantation ureter to bladder	Peritonitis

8. If function of the urethral sphincter muscles cannot be restored by vaginal plastic procedures, an attempt to establish urinary control by transplantation of adjacent muscles and fascia should be considered. A technique for this purpose recently described has been successful in nine out of ten cases operated upon by three gynecologists.

9. As a means of relieving urinary stress incontinence, transplantation of fascia should always be combined with vaginal plastic surgery. It should never be used as a substitute for the standard vaginal plastic procedures in use for the same purpose.

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899 PARK AVENUE

A GENERAL SURVEY OF THE VAGINAL SMEAR AND ITS USE IN RESEARCH AND DIAGNOSIS*

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IT IS really remarkable how often accidental happenings play an important role in our life, leading us into paths which determine our future course. Such an accidental event was the introduction of the vaginal smear in the study of the sex cycle of the guinea pig some thirty years ago.¹ At that time Dr. Charles R. Stockard and I were involved in the study of other problems of more general interest. Personally, I was planning to investigate further the problem of sex determination and sex control in the guinea pig.²

When the vaginal smear technique was first introduced in our laboratory in 1916, its usefulness in the study of problems related to the mammalian female sex cycle became immediately evident. Yet no one could, at that early date, foresee its remarkable potentialities and its steadfast and ever expanding growth. Its introduction as a general method of investigation marked an era of unparalleled progress in the field of mammalian sex physiology and sex hormonology.

These developments have gradually changed the course of events in our laboratory. More and more of our interest and time were taken by this work and by the many new problems emanating from it. Our fate was thus sealed, and the method which was meant to serve us in our studies became our own master. After almost thirty long years, I still find myself enslaved by it. In this short presentation I will endeavor to give you a brief account of some of its applications, more particularly of those related to the human female sex cycle, and to the diagnosis of uterine cancer.

The earliest attempts to apply the vaginal smear technique in a more comprehensive study and analysis of the menstrual and reproductive functions in the human did not appear to justify the expectations and hopes placed upon it after its successful application in some of the lower mammals. The striking sequence of clean-cut cytological changes observed and described in the vaginal fluid of the guinea pig and other rodents was found to be practically absent from the human vagina. It is, therefore, not surprising that a man of the broad vision and the great foresight of Dr. Edgar Allen took a decidedly pessimistic attitude by stating that tests on human vaginal smears showed no clear-cut changes as found in rats. He concluded that "in the primates, menstruation furnishes such a prominent milestone that vaginal smears seem of secondary importance for diagnosis."³

*Presented, by invitation, at a regular meeting of the Chicago Gynecological Society, April 20, 1945.

In contrast to the extensive cornification of the vaginal epithelium in the rodents and its massive desquamation sometimes in the form of a single sheath, the epithelium of the human vagina undergoes only a partial and incomplete cornification, and consequently, a partial desquamation of its more superficial layers. Furthermore, the study of biopsied human vaginal epithelium by a large number of investigators failed to result in a general agreement as to the extent of the epithelial denudation during the normal cycle, or the regularity in the appearance and the significance of the intraepithelial zone. Some even denied the presence of distinct cyclic changes. This latter view, however, appears to be rather extreme and based chiefly on negative findings, or, in some instances, on inadequate material. The existence of a vaginal epithelial rhythm has been demonstrated quite conclusively by the study of epithelial biopsies⁴ as well as of vaginal smears.⁵

The structural changes of the vaginal epithelium are particularly distinct during the period of high follicular activity prior to ovulation, and are reflected in the appearance of a characteristic smear type. Corresponding changes in the epithelium and the smear have been induced experimentally in lower mammals and in the human through the administration of estrogenic hormone.⁶ Ovulation results in a disruption of follicular growth and is revealed in the smear by distinct modifications in the form and the grouping of the exfoliated cells. However, these changes are not specific and are the result, not of the follicular rupture itself, but of the decrease in the secretion of estrin which follows disruption of the follicular secretory function. Therefore, the vaginal smear offers only indirect evidence as to ovulation and the time of its occurrence.

The use of the vaginal smear for determining the time of ovulation requires considerable training and experience. The interpretation of findings is often difficult. Local infections, bacterial or parasitic, causing leucorrhea tend to modify and obscure the normal picture. Sometimes the follicular reaction is weak and the postovulatory changes not very distinct. The persistence of numerous acidophilic cells for several days after ovulation is also disturbing. The decrease of these cells is usually gradual and, therefore, the recognition of the exact time of ovulation cannot be based solely on the numerical variations of the acidophilic cells. Other points and, more particularly, the changes in the morphology of the cells should be taken into consideration.

A complete evaluation of the normal sex cycle in women requires an examination of vaginal smears, not only during the follicular and postovulatory stages, but during all phases of the cycle. The luteal as well as the menstrual phase have their own distinctive cytology. With proper staining one can recognize the small endometrial cells and thus obtain information as to the extent of exfoliation of the uterine mucosa.

The endometrial cells may appear singly or in clusters of variable sizes. When the exfoliation is profuse, relatively large fragments of the mucosa or of the uterine glands may be found. Some characteristic structures are often seen towards the end of the menstrual flow. They consist of dense groups of

pyknotic cells surrounded by larger epithelial cells. Such cell groups are quite typical of the late exfoliative and the early regenerative stages of the menstrual phase.

The extent of the endometrial exfoliation and its duration vary greatly. Certain conditions, like retroversion of the uterus, may cause a prolongation of the exfoliative process. In women who had been subjected to repeated curettage, the exfoliation has been found to be somewhat scantier. In anovulatory cycles, or in bleedings induced by estrogenic or other therapy, the uterine desquamation is, as a rule, less conspicuous than in the normal cycle, and the cells tend to be smaller and more densely grouped.



Fig. 1.—Endocervical smear. Cervical secretion fixed with silver nitrate. Stained in hematoxylin and DL 8 A. Secretion appears in the form of anastomosing branches ($\times 200$).

In connection with the study and evaluation of the normal cycle, I want to mention two procedures developed in our laboratory which promise to be very helpful. One is a new standard method for staining vaginal smears which has the advantage also of staining glycogen. It provides a good differentiation of the various acidophilic and basophilic cells encountered in the smears and of essential tissues, more specifically of the connective tissue which takes a bright red color. Therefore, it can be used advantageously not only in smears, but also as a general tissue stain. In sections of the vagina, cervix, and uterus, by emphasizing glycogen, mucus, and cornification, it allows a better evaluation of the secretory activity of these organs and of their cyclic changes.

The second procedure consists in the demonstration of a secretion which stains brown or yellow with silver nitrate.⁷ When abundant, it tends to spread in the form of anastomosing branches with heavily indented leafy projections (Fig. 1). At other times it appears in round droplets of various sizes in single or bifurcated rods or in starlike formations (Fig. 2). It can be demonstrated only in dry smears which have not been fixed in the usual smear fixative consisting of 95 per cent alcohol and ether. It is very likely that it

represents a kind of crystallization of the cervical mucus, showing an amazing variability in form which is probably determined by corresponding changes in its viscosity. Physiologic variations in the consistency of the cervical mucus associated with the normal menstrual cycle and affecting the migration and survival of the spermatozoa have been conclusively proved.⁸ It appears that it is now possible to demonstrate such changes morphologically and with a greater accuracy.

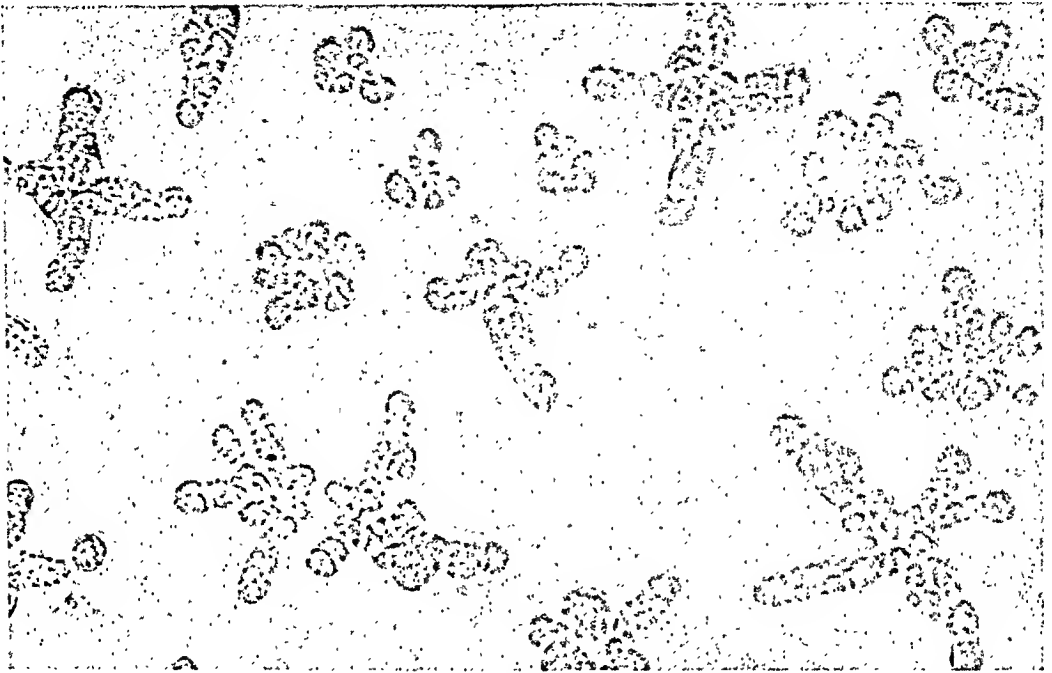


Fig. 2.—Endocervical smear. Cervical secretion fixed with silver nitrate. Stained in hematoxylin and DL 8 A. Secretion appears in the form of starlike structures ($\times 210$).

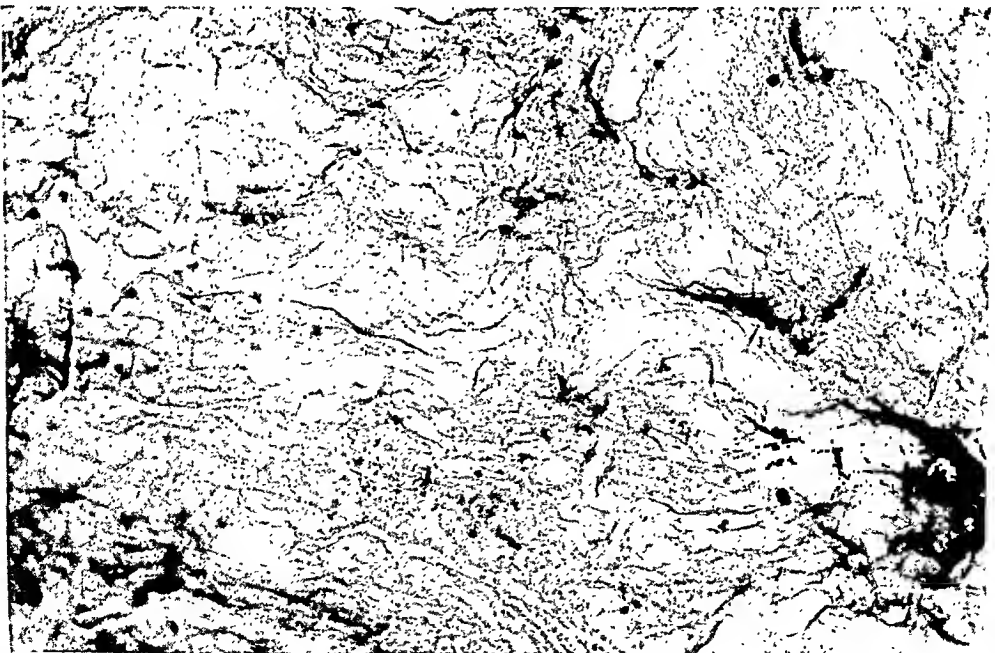


Fig. 3.—Endocervical smear. Cervical secretion fixed with alcohol-ether. Stained in hematoxylin and DL 8 A. Secretion looks like ordinary mucus ($\times 200$).

During the normal menstrual cycle this secretion becomes very typical and conspicuous near the peak of the follicular activity and at about the time of ovulation (Fig. 1; compare with Fig. 3). It decreases in amount and practically disappears in the vaginal smear during other stages of the cycle, during pregnancy, and in inactive states, such as amenorrhea or menopause. It shows considerable increase after administration of estrogenic hormone and constitutes an excellent criterion of the action of this hormone and of normal ovarian follicular activity. In smears prepared with fluid aspirated from the cervical canal, it is always found in a larger amount, and its presence can be demonstrated at all times with variations in quantity and form, depending upon the extent of follicular secretory function.

The use of smears prepared with fluid aspirated either from the cervical canal or from the uterine cavity with the aid of a thin metal cannula⁹ was advocated some two years ago by Dr. Marchetti and me.¹⁰ The procedure is simple and does not involve injury or trauma. The fixation and the staining technique are the same as in the vaginal smear.¹¹ Endometrial and endocervical smears are of value, not only in the study of the normal cycle and of problems relating to ovulation and sterility, but also in the diagnosis of fundal and endocervical neoplasms, and of some other conditions, like endometritis and hyperplasia. The functional changes of the cervix and of the endometrium are reflected in cytological modifications of their fluid content which can be estimated more accurately in endocervical and endometrial than in vaginal smears. We are now engaged in a detailed study of the cytology of the endometrial and endocervical fluid. This has to be done before we are in a position to use this new application to its full advantage.

One field in which our progress has been rather slow is that of diagnosis of pregnancy. Changes typical of gestation appear in the vaginal smear as early as the thirty-eighth or fortieth day and become more accentuated in advanced stages. The so-called "navicular" cells of pregnancy⁵ have some distinct traits which permit their recognition, but it is not always easy to differentiate them from some closely-resembling cell types found in other conditions, like amenorrheas. Furthermore, the typical smear picture of pregnancy may be distorted by local bacterial or parasitic infections causing leucorrhea, or by an excess of acidophilic cells.

Despite these shortcomings, the vaginal smear remains a useful guide in pregnancy. In normal gestation one can recognize some abnormal features suggestive of threatened abortion, such as blood, excessive mucus, pronounced acidophilia or intracellular blood-pigmentation. In abortions and ectopics, one usually finds moderate bleeding with high fibrination, marked acidophilia, and modified pregnancy or postpartum cells.

A point of interest and of some diagnostic value in abortions is the increase in the number and the phagocytic action of the histiocytes and the polymorphonuclears. They engulf and destroy not only bacteria and detritus, but also erythrocytes. The engulfment of erythrocytes by polymorphonuclears is a rather unusual occurrence in menstruation and in other conditions asso-

ciated with bleeding. In incomplete abortions a definite diagnosis can be established when trophoblastic or other placental or fetal cells are found.

As far back as 1923, when I first began a systematic study of human vaginal smears at the Woman's Hospital of New York City, I had been impressed by the strikingly abnormal features of cancer cells and of their nuclei, and I became aware of the diagnostic potentialities of the vaginal smear in malignant lesions of the uterus. In 1928, I reported these early observations in a short preliminary note.¹²

Despite the apparent importance of this work, I was compelled to neglect it for many years, as I was at that time involved in the study of other problems. One of them was that of senility and its effect upon the reproductive functions¹³ and upon the development of primary tumors¹⁴ in the guinea pig. In this animal, tumors usually appear after the fourth or fifth year, which would correspond to the forty-fifth or fiftieth year in human life. At the same time irregularities and disturbances of the sex cycle and of the reproductive functions begin to occur. The sex rhythm is retarded and the estrous intervals become gradually longer, but there is no actual interruption of rhythmic sexual phenomena as in the human, even at a very advanced age. However, the animals lose their ability to conceive, spontaneous abortions become more and more frequent and, though the cycle persists, the reproductive functions are gradually suppressed. Therefore, these animals have an actual climacteric period, but do not reach a state of complete cessation of their ovarian and estrous functions that would compare with menopause. It is of interest that atretic corpora lutea, which are very rare in the young animal, are found quite frequently in the senile guinea pig.

In 1932, I had the unique opportunity of observing the transition from the normal menstrual cycle into menopause in a woman whose cycles had been followed with daily vaginal smears uninterruptedly for many years.¹⁵ To my surprise, instead of reaching a state of complete cessation of her ovarian and uterine periodic functions, she continued having a series of irregular cycles for about four years before she entered a state of total inactivity, a real menopause. The uninterrupted daily examination of smears made possible the recognition and the interpretation of these atypical cycles. From time to time there was an appearance of a slowly developing and relatively prolonged follicular reaction, the end of which was marked by bleeding, sometimes scant, sometimes more profuse. These periods of ovarian activity were followed by longer and longer periods of inactivity, characterized by an atrophic type of smear, until a complete suppression of all cyclic functions finally occurred four years later. Whether this was an unusual occurrence, or whether it happens in many or all women entering their climacteric period, can be decided only on the basis of a larger number of observations.

In the field of human endocrinology, the vaginal smear was first applied on a larger scale in 1934, when I became associated with Dr. Ephraim Shorr and the Endocrine Clinic of the New York Hospital, where a large number of older menopausal and younger amenorrheic women were available for study.⁶

Dr. Shorr and I have been able to verify the appearance of spontaneous follicular reactions in women after menopause and to induce typical smear changes with adequate estrogenic therapy in both menopausal and amenorrheic women. The usual smear types encountered in menopause and amenorrhea have also been described.^{6, 16} The application of the smear test as a method of evaluating ovarian insufficiency and as a guide in hormonal therapy has since been greatly extended, and its value is now being generally recognized.

An excellent opportunity to resume the cancer work was offered to me in 1939 at the Woman's Clinic of the New York Hospital in cooperation with Dr. Herbert Traut, and later with Dr. Andrew Marchetti. Vaginal smears were introduced as a routine in practically all gynecologic patients of the Hospital. The results have already been published in a comprehensive monograph in the summer of 1943.¹⁷ This publication created considerable interest and soon the method began to be tested by other investigators.

Dr. Joe Vincent Meigs and Dr. Maurice Fremont-Smith and their collaborators of the Harvard Medical School were the first ones to apply this test on a larger scale. Their findings were published in 1943¹⁸ and were, in all essential points, in agreement with our observations. Since then, three more reports have appeared, one by Dr. J. Ernest Ayre¹⁹ of the Royal Victoria Hospital of Montreal, one by Jones, Neustaedter, and Mackenzie²⁰ of the Post-Graduate Hospital of New York, and one by Fremont-Smith, Graham, Janzen, and Meigs of Harvard.²¹

In this last article, a statistical evaluation of 813 cases is given. The total error in diagnosing cancer was 2.8 per cent. False negatives (that is to say, positive cases called negative) were 7.1 per cent, and false positives (that is, negative cases called positive) were 2.8 per cent. Dr. Jones and her co-workers have tabulated 434 cases, in 82 of which a final diagnosis of malignancy was established by biopsy. False negatives were 7 (all fundus), while false positives were 9 (five cervical and four fundal).

In a survey of 3,014 adult women, of whom 127 had carcinoma of the cervix and 53 carcinoma of the fundus, Dr. Traut and I reported¹⁷ failures of 3.2 per cent in the cervical group and 9.3 per cent in the endometrial group. Our statistics show that failure to recognize adenocarcinomas or adenomas of the endometrium is much more frequent than failure to recognize cervical carcinomas. All above-mentioned statistics were based exclusively on the use of vaginal smears. It is to be hoped that with the introduction and more general application of the endometrial smear technique,¹⁰ the failures in the fundal group will be notably reduced.

The high percentage of false positives reported by Dr. Jones and her co-workers indicates that we have to learn more about the reliability and the pathognomic value of some of our criteria. For this reason we strongly feel that this diagnostic procedure should be employed at present with great discretion, and that it should be entrusted to experienced pathologists.²² Smear reports should be conservatively worded, and the findings corroborated as often as possible by curettage or biopsy before any major operation is decided upon. No case should be reported as definitely positive unless the evidence is overwhelming.

False positives are undoubtedly the most serious failures, and our efforts should be directed toward reducing their number to the best of our ability. Missing a positive case is a less serious error, since everyone realizes that this

method of diagnosis is based on the recovery of exfoliated tumor cells which may be subject to considerable fluctuation. It has been noted that the rate of exfoliation in various types of carcinomas differs greatly, and furthermore, one could not expect to find an equally large number of exfoliated tumor cells in every slide. The smaller the number of smears available for study, the greater the probability of missing a positive case. If findings are negative, it is always advisable to repeat the smears. Endometrial or endocervical smears, in addition to the vaginal smears, are also advisable when the diagnosis is obscure.

Although the preparation and staining of smears is relatively easy,^{11, 17} their interpretation is rather difficult. It is based on cytological criteria and requires special study and training. The nuclear changes appear to be the most striking and the most characteristic. The nucleus tends to be large and out of proportion to the size of the cell. Many nuclei are hyperchromatic or may show fragmentation. The chromatin has frequently a granular aspect, or an arrangement suggestive of a prophase. Actual mitoses are rare. In certain types of cancer, the nucleoli are large and very conspicuous. Anisonucleosis and anisocytosis are often marked. The cytoplasm tends to be dense and basophilic. It may show pronounced vacuolation or it may contain inclusions of polymorphonuclears, lymphocytes, or plasma cells. In the cervical carcinomas, one often finds highly differentiated cells which acquire abnormal and bizarre forms. Many cells become elongated in the form of fibers, or take on a shape resembling a tadpole. In the squamous cell carcinomas acidophilia and cornification are quite pronounced.

The nuclear changes of cancer cells seem to offer the most reliable diagnostic criteria. One should refrain from basing a positive diagnosis exclusively on the presence of modified superficial cells. It is also unsafe to consider as absolutely conclusive the vacuolization of cells or their infiltration by leucocytes, as these changes may occasionally be found in other conditions, like hyperplasia, metaplasia, or endometritis.

Chronic cervical infections and parasites, like *Trichomonas* or *Monilia*, sometimes cause structural modifications of the superficial vaginal and cervical cells. This renders more difficult the recognition of the cancer cells, particularly when the exfoliation is scant, as in certain invasive forms of carcinoma. A crusade of the medical profession against chronic infections of the female genital tract would go a long way toward reducing unhealthy conditions which might favor the eventual appearance of cancerous lesions.

Lately, Dr. Victor Marshall, of the Department of Urology of Cornell Medical College and of New York Hospital, and I have been investigating the possibility of detecting carcinomas of the urinary tract in both men and women by examination of smears prepared from urine sediment. About 40 c.c. of voided, or preferably catheterized, urine was mixed with 10 c.c. of 95 per cent alcohol which fixes and preserves the cellular elements, and then centrifuged for about ten minutes. Smears were made of the sediment, fixed in alcohol-ether and stained in the same way as vaginal smears. So far, we have ex-

amined about 120 cases. The results have been very gratifying and have already been reported in a preliminary note.²³

Evidence is presented that neoplasms of the urinary organs, including bladder, prostate, and kidneys, can be detected by this method, which may prove to be helpful in diagnosing neoplasms of the urinary organs and in following up their treatment.

In concluding, I want to emphasize the fact that the smear method is morphologically sound, and its usefulness in endocrine and gynecologic investigation and diagnosis has been amply demonstrated. It has the advantage of being simple, short, and inexpensive. It can be repeated as often as necessary since it causes no inconvenience to the patient. In cancer diagnosis its reliability and value are being increasingly recognized, a notable point in its favor being that it offers positive evidence in early stages of malignancy before the appearance of definite clinical symptoms. It is also particularly adapted to the screening of a large number of women, as in cancer-prevention clinics.

As the method is more widely tested, the accumulating observations of experienced pathologists will further improve its diagnostic value by helping us to make a more effective use of our criteria.

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Discussion

DR. M. EDWARD DAVIS.—My interest in the cyclical changes in the vagina was initiated by Dr. Carl Hartman in 1935. I had the good fortune to spend that year in his laboratory at the Carnegie Institution of Embryology. The question of a cycle in the vag-

inal mucosa was still very debatable at that time. His monkey colony provided an excellent opportunity to study the vaginal changes in a primate under carefully controlled laboratory conditions. We devised a method for obtaining biopsies of the vagina at weekly intervals and we were able to correlate the histologic changes in the vaginal mucosa, the cellular changes in the vaginal fluid, and the cyclical changes in the ovary. A cycle could be demonstrated in the vagina which was dependent on the activity of the ovary.

Subsequently, the biopsy method was extended to the study of women at the Chicago Lying-in Hospital. The changes during the cycle, as well as in the menopausal period, were carefully studied and reported. The estrogenic treatment of postmenopausal vaginitis was a development of this work, and the method has found wide clinical application. The changes in the mucosa of the vagina during pregnancy, labor, and the postpartum period were followed by repeated biopsies in the same individual and these histologic studies correlated with vaginal smears.

We have had very little experience with vaginal smears in the diagnosis of cancer of the uterus. It is my impression that they may be a useful aid in our search for early neoplasm of the reproductive tract. Cancer clinics with properly trained personnel may be able to screen large numbers of women by routine vaginal smears, selecting the few who will need further investigation. The interpretation of these smears will become the task for competent histopathologists. No special stain will serve to identify the cancer cell for the inexperienced observer. Endometrial smears and urine smears may provide additional help in the early diagnosis of cancer.

DR. RACHMIEL LEVINE.—In the Department of Endocrinology of Michael Reese Hospital, we have followed several types of problems for the last five years by using the vaginal smear technique. As a result of studies involving various endocrine problems, such as menorrhagia, metrorrhagia and functional sterility; and of following normal cycles, it is our opinion that the most valuable function of the vaginal smear is to serve as an index of estrogenic activity. When there is normal estrogenic activity the smear contains large eosinophilic, so-called cornified cells. In the absence of estrogenic activity, or when it is very low, one finds the type of smear shown by Dr. Papanicolaou consisting of basal cells and leukocytes. In other words, one sees in the smear a reflection of the thin, atrophic basal layer of the mucosa. One sees that also in bleeding from an atrophic mucosa. One can see a high "estrogen" smear in bleeding due to a hypertrophic state of the endometrium. It is therefore possible to distinguish cases in which the estrogen activity is normal, supernormal, or below normal.

When it comes to the second of the ovarian hormones, progesterone, and its reflection in the smear, the data are not so clear. I would like to hear Dr. Papanicolaou's opinion whether progesterone by itself has a direct effect on the smear at all. In the second half of the cycle the smear is characterized by a folding and clumping of cells succeeded by leukocyte infiltration and later menstrual bleeding. A similar picture is presented even when no progesterone is present at all. Thus, when an ovariectomized woman is given estrogen and the mucosa is built up, and then the estrogen is withdrawn, the smears are difficult to differentiate from the second phase of a normal cycle when progesterone is being secreted. That may be why there is so much difficulty in establishing the smear typical of pregnancy. There is a high progesterone as well as estrogen level in pregnancy, and the two hormones acting together make it impossible to diagnose the smear correctly.

The point I would like to re-emphasize is the warning of Dr. Papanicolaou, that the technique of taking the smear is of prime importance, and that it has to be followed daily before one can use the smear as a diagnostic instrument. One smear taken at random is of little or no value in the diagnosis of sex-endocrine syndromes.

DR. JOHN F. SHEEHAN.—My interest in Dr. Papanicolaou's work is that of the general pathologist. If an attempt is made to introduce his method to the general practitioner, as a screening process for the detection of carcinoma of the uterus, the general pathologist will have to bear the brunt of the burden. My own experience with the method

has been sufficient to demonstrate that it has definite difficulties and can be time-consuming. However, it has not been extensive enough to evaluate the accuracy of the method.

The material studied consisted of smears of the vaginal fluid during the various phases of the menstrual cycle, the postmenopausal and postabortive states, and from cases of pathological endometrial hyperplasia (hyperestrinism), acute and chronic cervicitis, leiomyomas of the uterus, endometrial polyps, cysts of the ovaries, several squamous cell carcinomas of the cervix, several adenocarcinomas of the endometrium, and one pseudomucinous cystadenocarcinoma of the ovary emptying into the vagina through a colpotomy incision. All diagnoses were confirmed by biopsy, curettage, or the examination of the excised uterus and adnexa.

The difficulties of the vaginal smear method can be best appreciated by a comparison with those encountered in the examination of pleural and peritoneal fluids for cancer cells. With regard to these, even as late as 1933, Graham could state that, due to the use of smears, "the resulting uncertainties have bred a laboratory tradition highly suspicious of any attempt at their [tumor cells] positive identification." The situation has been greatly improved by the practice of centrifuging pleural and peritoneal fluids, and of subsequently treating the sediments as tissues, subjecting them to routine fixation, dehydration, clearing, and staining. The features considered diagnostic of malignancy in the cells in these sediments are: the presence of identifiable fragments of tumor tissue; mitoses in isolated cells or clumps of cells; irregularity in cellular size, particularly an increase in size; nuclear hyperchromatism; increased nuclear size; increased prominence of the nucleoli; the presence of multinucleated cells, tumor giant cells; and an increase in nuclear volume in comparison to the cytoplasmic. Fat droplets in the cytoplasm, vacuolation, and leucocytic invasion are not diagnostic (Graham). Even with the use of these criteria, the diagnosis is often difficult, despite the fact that the conditions in the serous cavities are relatively simple. Monoocytes and mesothelial cells are the chief sources of confusion.

The conditions in the female genital tract, on the other hand, are much more complex. Various types of epithelium are encountered. Normal hormonal influences, as well as hormonal imbalances and pregnancy, cause changes. Inflammation and benign tumors are commonly present. Hence, the sources of confusion are multiplied. Clumps of histiocytes, groups of endometrial cells, not always organoid, foreign body giant cells, and chorionic synechium may be present. As a result, the presence of clumps of cells are less diagnostic than in sediments of pleural and peritoneal fluids. Mitoses are not commonly encountered, even in cases of carcinoma. The diagnosis of carcinoma by the vaginal smear method must often rest on the evaluation of changes in single cells or small groups of cells. Dr. Papanicolaou uses the same criteria as those used in identifying tumor cells in pleural and peritoneal sediments, except that in certain cases of adenocarcinoma of the endometrium, according to Dr. Papanicolaou, the diagnosis is based on the presence of small dark-staining cells with nuclei almost black. Only a great deal of experience would enable one to identify such cells with any certainty. From the pathologist's viewpoint, such cells do not exhibit the usual microscopic signs of malignancy. Nuclear enlargement, hyperchromatism, and irregularity in size and shape may be found in some nonmalignant cells, such as irradiated normal epithelial cells, and hence lose some of their diagnostic value in the evaluation of cells found in the vaginal smear. Finally, the cells in these smears are not as clearly defined as they are in the beautiful drawings in Dr. Papanicolaou's book.

Since the pathologist in many hospitals has to make his diagnoses without the aid of clinical data, information which might be helpful in the evaluation of vaginal smears, such as a history of pregnancy or of a recent pregnancy, previous irradiation, menstrual dates, and the date of the menopause, would probably not be readily available. His task would be even more difficult as a result.

In the hands of experts the vaginal smear method has shown great promise, but even Dr. Papanicolaou admits 9.3 per cent failures in the endometrial group of cancers. This percentage would be much higher in the case of the average general pathologist at the present time.

In conclusion, let me restate that my material does not permit an evaluation of the accuracy of the vaginal smear method for the detection of cancer cells. That they can be identified has been definitely demonstrated by Dr. Papanicolaou. I have been able to recognize them in several of my cases and, with greater experience, will be more confident of observing them. My remarks are not to be construed as a criticism of the validity of the method. I am merely pointing out the difficulties encountered. Dr. Papanicolaou mentioned the possibilities in the use of endometrial rather than vaginal smears. The former should be much more satisfactory than the latter.

Personally, I do not believe that the time is ripe to launch the vaginal smear method as a screening process for carcinoma of the uterus. The method needs further evaluation; and the pathologists must be prepared on the method before success is assured for a screening program. It will not be easy for many pathologists to assemble enough material, sufficiently varied, to familiarize themselves with the method.

I have based these conclusions on the material which I have studied. I reserve the right to change my mind later when I have had more experience with the method.

DR. PHILIP H. SCHNEIDER.—I was much interested in many of Dr. Sheehan's remarks, because they bring up some points that I would like to emphasize. I shall discuss these points from the standpoint of the clinician.

In the first place, there are many important things about the preparation of the material which I know Dr. Papanicolaou did not have time to mention. It is very important that these smears are thin, that is, just a bit thicker than ordinary smears for a differential count. The smears must not be permitted to dry. They must be immediately fixed in equal parts of alcohol and ether to prevent disintegration of the nuclei and cells. The staining technique also is quite important.

It is obviously going to be impossible for the clinician to carry out this work himself. The load that our laboratories are now carrying will not permit them to give much assistance. The experience of Dr. Meigs in Boston gives us an idea of what should be done. Dr. Meigs has two clinicians who were trained under Dr. Papanicolaou and who do all the checking of these various smears. It is necessary to examine more than one smear, and more smears than obtained in one day if you have a suspicious-looking slide. It is only by so doing that the clinicians are going to have the benefit of the work done.

We have a technician at the Evanston Hospital who has been devoting most of her time during the past year attempting to learn the technique of staining and of interpreting the slides. We hope that eventually we will be able to interpret these slides with some degree of accuracy.

DR. PAPANICOLAOU (Closing).—The lantern slides of the colored drawings of normal and cancer cells which I have demonstrated have probably conveyed to some of you the impression that the recognition of all these cell types in smear preparations would be relatively simple and easy. Since this is not the case, I feel that I must apologize for having created such an erroneous impression through the projection of these slides. Dr. Schneider's remarks are fully justified. The actual reading of smears for the purpose of diagnosing cancer is not an easy task for any one who has had no special training in this new diagnostic procedure. The eagerness of a pathologist or a technician to apply it before acquiring an adequate training would undoubtedly lead to many errors and disappointments and would finally result in a definitely pessimistic attitude like the one expressed by Dr. Sheehan.

An adequate preliminary training could be acquired within the relatively short period of a few weeks. A number of pathologists and technicians have already been trained in our laboratory. The Department of Health of the Commonwealth of Massachusetts has entrusted us with the training of some members of its scientific staff to enable them to conduct a thorough investigation of the usefulness of the smear method as a public health measure.

The application of the smear technique to centrifuged urine for the diagnosis of cancers of the urinary tract led to very gratifying results. The identification of cancer cells in the urine sediment smears is, in fact, easier than in the vaginal and endometrial smears, because of the smaller number and variety of the exfoliated normal cells. Furthermore, for evaluating properly a vaginal or an endometrial smear it is always wise, if not essential, to have information on certain points, namely, the age of the patient, and the date of the last menstruation. For the urine specimens no information except the name of the patient was requested.

A similar technique works well also with the pleural and peritoneal fluids. An important point is the immediate fixation of the fluid and the subsequent fixation of the smear with alcohol and alcohol-ether respectively. The prevention of drying of the smears and their proper staining are also essential.

With regard to Dr. Levine's question as to the effect of the corpus luteum hormone, I may say that its action upon the epithelial tissues is not as definite as that of the estrogenic hormone. It was with a great deal of surprise that I noticed recently marked changes in the cytology of the urine sediment after administration of estrogenic therapy in a man with prostatic carcinoma. The cancerous exfoliation remained unaffected, but the normal cells showed striking changes.

PREMATURE DELIVERY, CAUSES AND RESULTS

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IT IS estimated¹ that prematurity is the primary cause of 18.5 per cent of all neonatal deaths, and an associated factor in another 25 per cent. The credit for the decrease in mortality in premature infants in recent years belongs, in most part, to the pediatrician. However, the responsibility for the prevention of premature delivery, and for the delivery of premature infants in the best possible condition rests upon the obstetrician. It is of some interest, therefore, to study the causes and results of premature delivery.

We present here a study of 941 consecutive premature deliveries which occurred on the ward and private services of the Woman's Clinic of the New York Hospital from Sept. 1, 1932, through Dec. 31, 1943. We have defined the premature infant as one whose birth weight is between 1,500 and 2,499 grams, or whose length is between 35 and 44.9 centimeters, regardless of the duration of pregnancy. The premature deliveries represented 2.95 per cent of the total deliveries during the same period. The annual incidence of premature deliveries did not vary significantly over the years studied, and there was no significant trend in the seasonal incidence.

Before discussing the specific causes of premature deliveries, it is well to note briefly the type of patient in which they occur, and some of the general factors which may have an indirect bearing upon the individual cases. The age distribution of this group was identical with that of the clinic as a whole. The average age in the premature group was 28 years, while the average clinic age was 27.5 years. The racial incidence in the premature group was not significantly different from that of the general clinic population. Negroes were slightly more frequent in the premature group.

Overwork has been mentioned by some as predisposing to premature labor. We have no figures to estimate this factor. However, the type of registration, ward or private, was approximately the same in this series as in the entire clinic. This would indicate something of the income group from which these patients are drawn, though not necessarily the amount of physical activity in which they indulged.

The relative fertility of the group cannot be evaluated accurately, as we have no data concerning the use of contraceptives by our patients. However, the average duration of marriage in the primigravidas was 2.5 years. In 9.7 per cent of the primigravidas, the marriage was of over four years' duration. These figures do not suggest that sterility is related to premature labor.

The previous obstetric history of these patients is summarized in Table I.

TABLE I. TYPE OF PATIENT IN PREMATURE DELIVERIES

	INCIDENCE (PER CENT)	
	PREMATURE GROUP	TOTAL CLINIC
Age	28.0 years	27.5 years
Race		
Negro	8.8	4.4
White	91.2	95.6
Registration		
Ward	81.4	78.2
Private	18.6	21.8
Previous obstetric history		
Primiparas	53.4	51.8
Multiparas	46.6	48.2
Primigravidas	44.4	48.2
Previous abortions		
Spontaneous	16.7	15.6
Induced	5.2	3.0
Previous premature deliveries	12.4	4.0
Sex of infant		
Male	46.4	52.1
Female	53.6	47.9

We note that the incidence of previous abortions is essentially the same as in the clinic. The number of previous premature deliveries is tripled. A few of these patients had as many as five previous premature deliveries.

The sex ratio of the premature infants was slightly altered, the females predominating. This has been found to be the case in other studies of premature infants.²

Causes of Premature Delivery

The causes for the onset of premature labor may be considered as maternal, fetal, or placental. Table II shows the distribution of the major causes

TABLE II. CAUSES OF PREMATURE DELIVERY

	INCIDENCE IN PREMATURE GROUP; NO OTHER FACTOR	INCIDENCE OF CONDITION	
		PREMATURE GROUP TOTAL	TOTAL CLINIC
Maternal			
Toxemia, all types	8.5	21.7	7.3
Syphilis	0.5	1.9	1.7
Pulmonary disease	1.0	1.4	--
Pyelitis	0.6	1.2	--
Pelvic pathology			
Myoma uteri	2.1	3.4	1.3
Bicornuate uterus	0.5	0.7	--
Ovarian cyst	0.1	0.3	--
Previous pelvic surgery	2.0	7.7	4.8
Other	0.8	2.4	--
Cardiac disease	1.5	3.4	3.0
Fetal			
Deadborn macerated infant	3.9	10.1	0.5
Twins	5.3	7.7	1.2
Triplets	0.3	0.3	0.009
Congenital abnormality	2.8	4.2	0.5
Hydramnios	0.2	1.2	0.3
Placental			
Placenta previa	0.6	3.8	0.5
Premature separation	1.8	4.3	0.4
Premature rupture of the membranes	16.8	33.7	24.5

in this series. In 20.0 per cent of our cases, premature delivery was the result of induced labor, or of elective cesarean section. These cases are not included in the figures dealing with spontaneous premature labor.

TABLE III. CLASSIFICATION OF TOXEMIAS

	INCIDENCE	
	PREMATURE GROUP	TOTAL CLINIC
Renal disease	3.7	0.26
Mild pre-eclampsia	6.5	3.45
Severe pre-eclampsia	5.3	0.75
Eclampsia	1.1	0.20
Acute yellow atrophy of the liver	0.1	0.01
Unclassified	3.5	1.53
Hypertensive disease	1.5	1.09
Total	21.7	7.29

The toxemias of pregnancy are generally considered an important cause of premature labor. Table III shows the classification of the toxemias in this group, compared with that of the entire clinic. The total incidence of toxemias in this series was 21.7 per cent, a figure which is in striking contrast to the clinic figure of 7.29 per cent. This increase is noted in all types of toxemia except hypertensive disease. Further analysis of the toxemias shows that in the majority of cases, premature labor was associated with factors other than the toxemia.

TABLE IV. INCIDENCE OF OTHER COMPLICATIONS IN CASES OF TOXEMIA

No other factor	38.7
Section or induced labor	31.9
Deadborn macerated infant	12.7
Twins	5.1
Premature separation of placenta	4.9
Myoma uteri	1.5
Hydramnios	1.5
Syphilis	1.6
Other	2.1
	100.0

From Table IV we may conclude that although toxemias are a major cause of prematurity, they are so chiefly because of their associated high incidence of induced, or artificial delivery before term, intrauterine death of the fetus, premature separation of the placenta, hydramnios, and twins. Toxemias per se account for a definite but relatively small percentage (8.5 per cent) of premature labors.

Formerly, maternal syphilis has been a more important cause of premature labor than the toxemias of pregnancy. In the past twelve years in this clinic, the incidence of syphilis has been relatively low (1.7 per cent). Where it is found, adequate therapy has been promptly administered in most cases. In the premature deliveries, syphilis was present in 1.9 per cent of cases. Of this group (eighteen patients), 50 per cent of the infants were deadborn macerated. Of these deadborn infants, only three were definitely syphilitic. Three deaths were presumably due to placenta previa, with no evidence of syphilis, and three were associated with toxemias.

Pulmonary complications were present in 1.4 per cent of the cases. It appears that they are rarely the primary cause of premature labor, with the notable exceptions of pneumonia, and severe active tuberculosis. All of these cases had acute febrile reactions which might account for the premature labor.

Pyelitis was found in 12 cases in the series. These cases occurred in the earlier years of the study, when our management of pyelitis was much less satisfactory than it has been since the advent of sulfonamide therapy. Pyelitis, with an acute febrile reaction, was the apparent cause of premature labor in six cases. In the other six cases, labor was induced, or elective cesarean section was performed because of pyelitis.

Pelvic pathology was present in 4.4 per cent of our cases. Myoma uteri was the most frequent finding, occurring in 3.4 per cent of the series, or nearly three times as frequently as in the general clinic. It has been shown by others³ that premature labors are more frequent in patients with myoma uteri, especially the larger ones. In most of the patients with myomas, there was no other explanation for the onset of premature labor. There were seven cases of bicornuate uterus in the premature series. Of these, five went into premature labor spontaneously with no other apparent cause, and two had cesarean sections because of complications of pregnancy. Of the three ovarian cysts, only two were large enough to be of significance. One of these measured 12 centimeters in diameter. The patient went into labor spontaneously, and was delivered by cesarean section when it was found that the cyst was blocking the pelvic inlet. The second large cyst was in a syphilitic patient, with a dead-born syphilitic infant. The third patient had a very small cyst, and a twin pregnancy.

In the premature series, 72 cases, or 7.7 per cent, had had previous major pelvic operations. The most common operations were cesarean section, and salpingo-oophorectomy. In the group of 21 cases which had had previous sections, premature delivery was accounted for by other causes in all but two instances. In patients with previous myomectomy or suspension of the uterus, these operations were the sole possible causes in only one-quarter of the cases. Where salpingo-oophorectomy had been performed, 50 per cent of the patients had no factor other than the previous operation. There were only four cases of previous amputations of the cervix. In all of these, the operation was thought to be responsible for the onset of premature labor.

There were a few instances of other conditions which may have played a role in premature labor. Two unexplained premature labors occurred in psychotic patients. There were single cases of arachnoiditis, epilepsy, diabetes, rheumatoid arthritis, and achondroplastic dwarfism, where these conditions were the only remarkable factors. In one case, overwork was recorded as the cause of the onset of premature labor. One labor was induced because of myasthenia gravis. One elective section was performed because of renal tuberculosis. Another patient had two premature elective sections because of a pelvic kidney, spina bifida, and cord bladder. In addition, there were several cases of diabetes with deadborn macerated infants. There was one case each

of cirrhosis of the liver, toxic goiter, appendicitis, and leucemia. Each of these had a concurrent toxemia of pregnancy, so that the role of each condition in premature labor was obscured.

It has been shown previously⁴ that heart disease does not affect fetal mortality, except through an increased incidence of therapeutic abortions. In the present series, we find that the incidence of cardiac disease is essentially the same as in the clinic. It was noted that in most of the cases where cardiac disease was the sole possible precipitating factor, the functional impairment was mild (Class I or II). It is probable that in these cases heart disease was merely an incidental finding. In three cases, however, heart disease was more directly related to prematurity. Two of these developed subacute bacterial endocarditis, with acutely febrile courses, prior to the onset of labor. In both of these, there was no other cause for premature labor. The third had an elective cesarean section because of heart disease.

The fetal causes of premature labor may be classified as intrauterine death of the fetus, multiple pregnancy, congenital abnormality, and hydramnios. Reference to Table II will show that all of these conditions are much more frequent in premature infants than in the whole clinic. We have included intrauterine death as fetal rather than a maternal cause of premature labor, since a fetus which dies in utero before term will be delivered as a premature according to weight, regardless of the date of delivery. The cases of deadborn macerated infants represent an interesting group. In thirty-seven cases, there was no other complication present. In these cases, the cause of death was unknown in all but six where cord accidents were noted. In the other cases, the autopsy findings were not helpful due to advanced autolysis of the cells. The toxemias of pregnancy were associated with 30.7 per cent of the deadborn macerated group. Placenta previa and premature separation of the placenta accounted for a smaller number.

The cases of multiple pregnancy are important in that they represent the second most frequent cause of prematurity (7.7 per cent). They are associated with a large incidence of toxemia, as would be expected.

Congenital abnormalities were found in a high percentage of the total series. The ones listed include only those abnormalities of major significance, such as anencephaly, hydrocephaly, and congenital abnormalities incompatible with life. It is not surprising that over one-third of these were deadborn.

Hydramnios was recorded in eleven cases. In five of these the infant was anencephalic. Table V shows the relationship of fetal and maternal complications in this series.

In order to determine the role of the placenta in premature labor, we have studied the pathologist's report in each case. In this clinic, the placenta is examined grossly and microscopically in all cases of premature labor. Table VI summarizes the more important findings in this series, compared with those in a series of 1,500 placentas studied in this clinic.⁵ In this study we find placenta previa in 3.8 per cent of cases, and premature separation of the placenta in 4.3 per cent. This is compared with the clinic figures of 0.48 per cent,

TABLE V. FETAL AND MATERNAL COMPLICATIONS

	INCIDENCE IN TOTAL SERIES			
	MULTIPLE PREGNANCY	DEADBORN MACERATED	CONGENITAL ABNORMALITY	HYDRAMNIOS
No other factor	5.3	3.9	1.3	0.2
Toxemia	1.1	3.1	0.3	0.1
Syphilis	0.0	0.3	0.0	0.0
Placenta previa or premature separation	0.2	1.4	0.2	0.0
Multiple pregnancy	--	0.3	0.1	0.0
Deadborn	0.3	--	1.8	0.1
Congenital abnormality	0.1	0.3	--	0.5
Hydramnios	0.0	0.1	0.5	--
Other	0.7	0.7	0.0	0.3
Total	7.7	10.1	4.2	1.2

TABLE VI. PLACENTAL PATHOLOGY

	INCIDENCE OF LESION				
	TOTAL CLINIC	TOTAL PREMATURE SERIES	PREMATURE + TOXEMIA	PREMATURE + SYPHILIS	PREMATURE DEADBORN MACERATED INFANTS
Normal placenta	77.8	65.1	45.0	11.0	13.6
Placental infarcts	18.0	13.3	33.7	28.0	24.2
Premature separation	0.5	4.3	4.8	0.0	11.0
Placenta previa	0.4	3.8	1.0	17.0	2.1
Syphilitic placenta	1.1	0.5	1.0	28.0	5.2
Questionably syphilitic		1.7	1.0	5.0	7.3
Other	2.2	11.3	13.5	11.0	36.6

and 0.36 per cent, respectively. The incidence of these placental accidents is increased tenfold in our series. In these cases, premature delivery was the result of induced labor, or elective cesarean section in 72 per cent of the cases of placenta previa and in 50 per cent of the cases of premature separation of the placenta. Thus, their role in premature delivery is chiefly that of forcing the hand of the obstetrician rather than actually precipitating the labor. It is also of interest that one-quarter of the cases of premature separation of the placenta were associated with toxemias of pregnancy. With the exception of these two important factors, it is difficult to evaluate the role of the placenta.

The microscopic findings in the placentas reveal an incidence of infarcts and degenerative lesions of various types which is comparable to that in the general clinic. The number of infarcts in the patients with toxemias is increased, as was noted by Traut and Kuder in their study of placentas. There are also more infarcts among the patients with deadborn macerated infants, but this is due to the large number of toxemia patients in this group. There were only 5 cases where a positive diagnosis of syphilis was made. These were all in syphilitic patients. In a number of instances, a diagnosis of questionable syphilis was made where syphilis was not present.

The role of premature rupture of the membranes in premature labor is difficult to evaluate. In this series, premature rupture of the membranes at or before the onset of labor was found in 33.7 per cent of cases, a figure which is somewhat higher than the clinic incidence of 24.5 per cent. In a series of

cases of premature rupture of the membranes from the general clinic population, the incidence of premature labor was found to be 4.6 per cent, which is, again, higher than the total incidence of prematurity. These figures both suggest that premature rupture of the membranes, in some cases at least, is a precipitating factor of premature labor, rather than merely an incident in its course. In 20.2 per cent of this series, premature rupture of the membranes was the only complication present. If we exclude from this group the cases where rupture of the membranes was coincident with the onset of labor and where it may reasonably be presumed that the mechanism of labor had been mobilized prior to their rupture, we find that 16.8 per cent of our cases may be attributed to premature rupture of the membranes. A small number, 3.9 per cent, of these received medical inductions because of ruptured membranes. Since these undoubtedly would have gone into labor spontaneously within a short time, they are not excluded from the group.

Lastly, we must consider the group of patients in whom there was no apparent cause for premature labor. When we compare the average weight distribution of the infants in these cases with the total group, we find that they are somewhat heavier. The relation of the date of delivery to the expected date of confinement shows that these infants are born closer to term, as calculated from the last menstrual period, than the average premature in the series. These findings would suggest that a certain number of these infants who are classified by definition as premature, are actually full-term infants, who, for unknown reasons, have failed to attain the weight of 2,500 grams. The incidence of previous premature deliveries in this group was 11.8 per cent, which does not differ significantly from that in the whole series, 12.4 per cent. Apparently, habitual premature labor is not related to these cases.

Obstetric Factors

The obstetric management and complications at the time of delivery have as important a bearing on the end results of premature delivery as do the precipitating factors. Table VII shows the type of presentation found in this series.

TABLE VII. PRESENTATION

	INCIDENCE	
	TOTAL CLINIC	PREMATURE GROUP
Vertex	94.3	75.5
Breech	4.4	16.0
Face	0.3	1.0
Transverse	0.3	1.5
Compound	0.1	0.7
Unknown	0.6	5.3

We find that the incidence of abnormal presentations is markedly increased in the premature infants. It is well known that breech presentation is more frequent in the antenatal period than at term. Hence it is not surprising to find an increase in breech and other abnormal presentations in infants delivered before term. There seems no reason to assume that these abnormal presentations are a cause of the premature labor.

As would be expected, the duration of labor in the premature group is shorter than the average. Primiparas were found to have an average duration of labor of 12.9 hours, and multiparas, 9.4 hours, compared with the general clinic figures of 18 and 12 hours, respectively. The frequency of precipitate labor of three hours or less was 10.0 per cent, whereas, in the whole clinic, it is 6.1 per cent. Prolonged labor (30 hours or over) occurred in 4.3 per cent of our cases, compared with the clinic figure of 9.1 per cent.

The type of delivery in these cases is compared to that of the entire clinic in Table VIII.

TABLE VIII. TYPE OF DELIVERY

	INCIDENCE	
	TOTAL CLINIC	PREMATURE GROUP
Spontaneous	77.2	72.1
Low forceps	11.4	5.3
Midforceps	3.7	0.5
High forceps	0.1	0.0
Breech extraction	4.1	13.1
Version & extraction	0.5	2.5
Section	3.0	6.5

In this clinic, it is felt that a spontaneous delivery, with a deep episiotomy, is the procedure of choice for a premature infant, and an attempt is made to adhere to this policy wherever possible. For this reason, and because of the relatively short second stage in premature labors, we find a low incidence of forceps deliveries in this series. Because of the high incidence of breech presentation, we naturally have a higher incidence of breech extractions. A delivery is described as a "breech extraction" whenever the Mauriceau-Smellie-Veit maneuver is employed. The increase in version and extraction is accounted for by the higher incidence of transverse and compound presentations and by the fact that version is frequently performed upon the second twin. Cesarean section was performed more than twice as frequently as in the general clinic. Two-thirds of these sections were performed because of placenta previa, premature separation of the placenta, or toxemia of pregnancy.

Episiotomy was employed in only 28.3 per cent of the premature deliveries, compared with 43.3 per cent in the total clinic. Frequently, there is little time for an episiotomy in a premature delivery. However, in the last three years of this study, the use of episiotomy increased to 42.3 per cent, as a more deliberate effort was made to perform an episiotomy in every premature delivery.

It is generally believed that analgesic agents, especially morphine, should be used sparingly in premature labors. We find that 65.1 per cent of our cases received no analgesia during labor. Twenty per cent received morphine, alone or in combination with other drugs, and the remainder, 14.3 per cent, were given such medications as rectal ether, nembutal, and scopolamine. At the time of delivery, nitrous oxide, oxygen, and ether were given for anesthesia in 78.3 per cent of the cases. Cyclopropane or ethylene were used in only 1.2 per cent. Local anesthesia alone was used in 4.9 per cent, and 15.6 per cent received no anesthesia. In the last two years of the study, the use of local anes-

thetia has increased. Probably this is one of the best anesthetics for premature delivery, but, unfortunately, there is not always time for a pudendal block or local infiltration during the short second stages of these deliveries.

Results

The gross and the corrected infantile mortality of premature infants delivered at this clinic have shown a steady decline during the past 10 years, as shown in Fig. 1. The gross infantile mortality includes all deadborn and still-born infants and those who died during the neonatal period. The corrected mortality rate excludes from this figure all deadborn macerated infants and those with congenital abnormalities incompatible with life. The reasons for

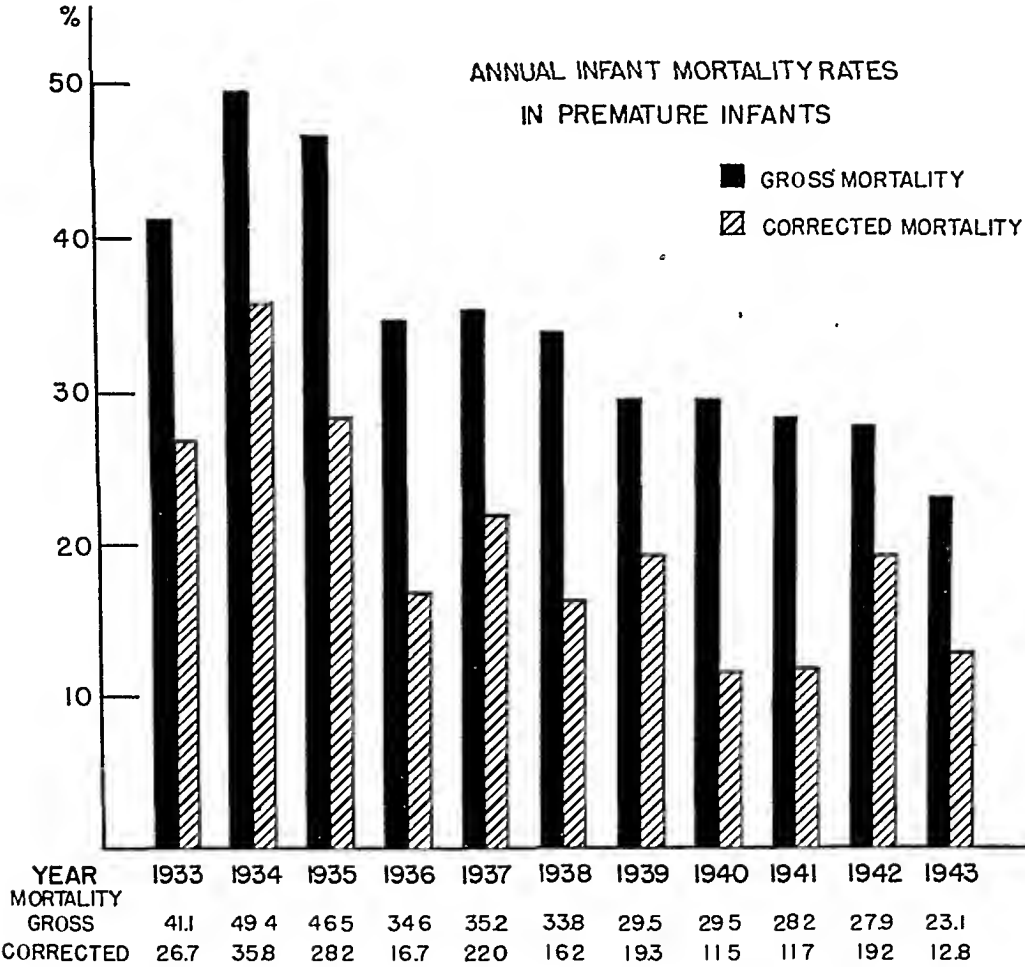


Fig. 1.

the decrease in mortality are manifold. We have attempted to observe certain precautions in all cases of premature labor. When a patient is admitted to this hospital in premature labor, the premature nursery is notified immediately and an incubator is prepared for the reception of the infant. During the course of labor, morphine is withheld and other analgesic agents are used sparingly. At the time of delivery, an episiotomy is performed, if possible. At birth, the infant is given prompt oxygen therapy if it is needed, and recently,

an injection of vitamin K. The infant is then transferred to the pediatric service without physical examination and with a minimum of handling.

The most important factor in the mortality of the premature infant is the birth weight. This has been amply demonstrated in the literature^{2, 6, 7} and our figures correspond with what has been shown by others, namely, that the mortality varies inversely with the weight (Fig. 2). Because this factor must be taken into consideration at all times in a study of premature infants, we have analyzed the mortality in each instance according to weight groups. In most instances the mortality-weight curves corresponded with the average total mortality for the group under consideration.

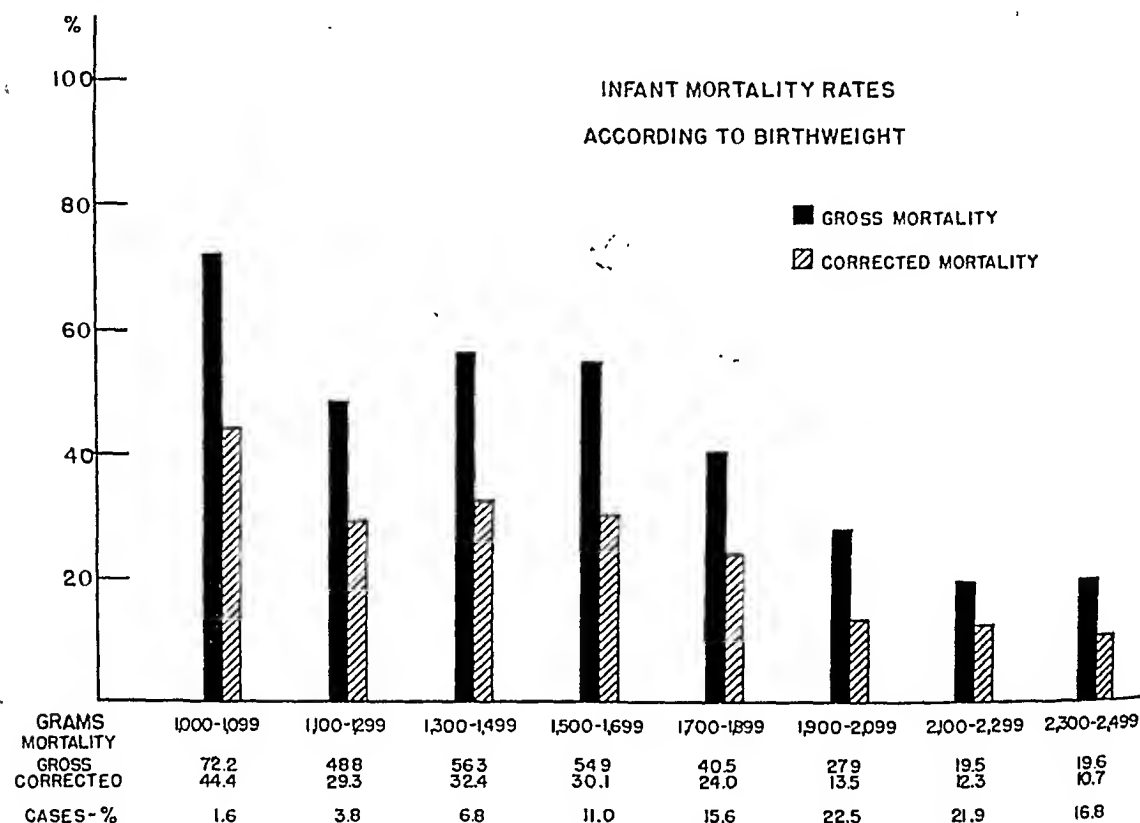


Fig. 2.

A study of the effect of some of the antenatal factors which influence the fetal mortality shows that the gross mortality is increased in all of the maternal complications which may be considered precipitating factors of premature delivery.

In the toxemias of pregnancy, a large part of the fetal mortality is accounted for by the number of deadborn infants. The corrected infantile mortality is actually lower than that for the entire group. This lower mortality in living infants is found in the cases of mild pre-eclampsia and unclassified toxemias. In severe pre-eclampsia and hypertensive disease, the corrected mortality is the same as for the whole series. In cases of renal disease, the gross and the corrected mortalities, even when corrected for the weight factor, are substantially higher than the total mortality.

TABLE IX. FETAL MORTALITY IN COMPLICATED PREGNANCIES

	INCIDENCE		
	GROSS FETAL MORTALITY	CORRECTED FETAL MORTALITY	SURVIVAL RATE
Entire group	33.3	18.8	66.7
Toxemias—all types	37.0	16.1	63.0
Mild pre-eclampsia	29.8	10.4	70.2
Severe pre-eclampsia and eclampsia	39.3	18.0	60.7
Unclassified	33.3	9.1	66.7
Hypertensive disease	35.2	17.6	64.8
Renal disease	51.5	30.3	48.5
Multiple pregnancy	35.9	28.1	64.1
Placenta previa	57.9	34.2	42.1
Premature separation of placenta	73.0	16.2	27.0
Premature rupture of the membranes	13.1	11.5	86.9
No complication	15.8	15.0	84.2

The gross and corrected mortality rates in cases of twins was slightly increased. This may be accounted for in part by the higher incidence of breech extraction and version, and extraction in multiple pregnancies.

The gross mortality rate in placenta previa and premature separation of the placenta was naturally very high. In premature separation of the placenta, it is noted that the survival of living infants was about the same as for the entire group. In cases of placenta previa, the corrected mortality is higher.

In the cases where there was no apparent cause for premature labor, or none other than premature rupture of the membranes, the mortality, both gross and corrected, was markedly decreased. This is accounted for partly by the fact that these were all uncomplicated cases, and partly by the higher weight groups in which these infants were found.

The value of some of our obstetric procedures may be judged by an analysis of their relation to fetal mortality. Table X summarizes the more important findings.

TABLE X. OBSTETRIC FACTORS IN FETAL MORTALITY

	NUMBER OF CASES	INCIDENCE		
		GROSS FETAL MORTALITY	CORRECTED FETAL MORTALITY	SURVIVAL RATE
Duration of Labor (Cesarean Sections Excluded)				
Precipitate	101	29.7	14.9	70.3
Average	813	32.7	17.7	67.3
Prolonged	42	33.3	16.7	66.7
Type of delivery				
Spontaneous	729	29.1	15.3	70.7
Low forceps	54	26.0	16.7	74.0
Midforceps	5	20.0	20.0	80.0
Breech extraction	135	46.3	31.6	53.7
Version and extraction	24	58.3	20.8	41.7
Cesarean section	71	47.0	29.4	53.0
Perineum (Spontaneous Deliveries Only)				
Episiotomy	189	14.8	12.2	85.2
Intact	389	33.4	16.2	66.6
Laceration	100	29.0	17.0	71.0
Analgesia				
Morphine	200	39.5	23.0	60.5
Other	143	32.2	18.2	71.3

As we would expect, the mortality rises with the duration of labor. We note that the lowest mortality was found in the precipitate labors of three hours or less. This appears even without correction for the very high percentage of small prematures found in this group. The average labors and the prolonged labors of over 30 hours showed about the same mortality rate. However, there were only a few prolonged labors, so that no valid conclusion can be drawn from the figures.

The mortality was increased in operative deliveries as compared with the spontaneous group. We see in Table X that the mortality in breech extraction, version and extraction, and midforceps delivery, was very high. In cesarean sections, the high mortality is accounted for by the high incidence of maternal complications which indicated the sections. In the low forceps deliveries, however, there was no significant increase in the corrected mortality, and the gross mortality was actually lower than in spontaneous deliveries. This finding becomes more significant when we remember that, in this clinic, low forceps are not used routinely for delivery of premature infants, and that in 50 per cent of these cases forceps were used because of fetal distress. The total number of low forceps deliveries was too small to draw any definite conclusions, but the results in these cases would suggest that they certainly have had no harmful effects, and may be of some value in protecting the premature head at the time of delivery.

The use of episiotomy has very definitely decreased the fetal mortality, as shown in Table X. Its effect is greatest in the higher weight groups where the larger head is subjected to more trauma if an episiotomy is not performed. In the lower weight groups, the trauma of delivery through an intact perineum is less, and the use of episiotomy was less frequent due to the number of precipitate deliveries.

Morphine was given to 20 per cent of these patients. In many cases it was undoubtedly given in an effort to prevent labor. The cases where it was given as a part of the modified Stroganoff treatment for pre-eclampsia were omitted from the series. Our figures show a definite increase in corrected fetal mortality where morphine was administered, compared with cases where other analgesic agents were used, and with the entire group. It is difficult to evaluate the significance of these findings accurately, but they suggest that morphine should be avoided wherever possible.

A study of the fetal mortality with different types of anesthesia showed that the total mortality is about the same whether inhalation anesthesia is used or not. The group which received no anesthesia contained a large number of very small infants, who were delivered precipitately. There were only a few cases where local anesthesia was used, since this has become popular in recent years. The figures in this group are not significant but its continued use and further study of its effects are certainly warranted.

The cause of death in these cases is summarized in Table XI. The dead-born macerated infants and those who died of prematurity and atelectasis naturally predominate in this group. The incidence of infection in the infant as a cause of neonatal death is increased when compared with figures from the

TABLE XI. DISTRIBUTION OF CAUSES IN 339 CASES OF FETAL AND NEONATAL DEATHS

CAUSES	INCIDENCE
Deadborn, cause unknown	29.5
Prematurity alone	17.1
Prematurity and atelectasis	15.8
Congenital abnormality	14.0
Intracranial hemorrhage	11.7
Infection	9.8
Syphilis	0.9
Erythroblastosis	0.9
Diabetes	0.3

total clinic deliveries.¹ The incidence of intracranial hemorrhage does not differ significantly from that found by D'Esopo and Marehetti¹ in their series of neonatal deaths.

Brief mention must be made of the maternal outcome in these cases of premature delivery. The maternal morbidity rate was 15.7 per cent. Puerperal infection was present in 10.4 per cent of the cases. These rates are considerably higher than in the general clinic where maternal morbidity is found in 9.4 per cent of cases, and puerperal infection in 7.2 per cent. This increase may be attributed partly to the large number of operative deliveries. The incidence of postpartum hemorrhage was also increased from 1.7 per cent in the total clinic to 2.6 per cent in the premature series. There were many cases of retained placenta with manual removal. These factors also tend to increase the morbidity rates.

There were five maternal deaths in the group. Two of these were due to pneumonia before the advent of sulfonamide therapy. Two were due to embolism and one to peritonitis.

Discussion

We have seen that the incidence of premature delivery has remained constant over the past twelve years. Apparently, little progress has been made toward its prevention. This is not surprising, since we have found that the most important causes of premature delivery are beyond the control of the obstetrician. The occurrence of multiple pregnancies and congenital anomalies cannot be influenced. The management of placenta previa and premature separation of the placenta must take into account the serious risk to the mother. In these cases the infant is often dead before safe delivery can be effected. In toxemias of pregnancy, again, the maternal risk is a serious factor. Here, radical therapy gives us a premature infant, while conservative therapy may give us a dead one. Only the discovery of the cause and specific cure of toxemias can solve this dilemma. The chief contributions which the physician may offer are in the control of syphilis and the prevention and management of such diseases as pneumonia and pyelitis.

We have made definite progress, however, in improving the results of premature delivery. The decreasing infantile mortality in our series reflects many factors. From the obstetric point of view, the type of delivery is of greatest importance in the outcome of the case. Spontaneous delivery with episiotomy has yielded very satisfactory results in our hands. There is some

evidence that the use of outlet forceps may be of value and further study of this problem seems warranted. The use of morphine should be avoided wherever possible and local anesthesia may prove more desirable than general. Finally, the close cooperation of the obstetrician and pediatrician in giving the premature infant the prompt and careful attention it requires is the most important factor in reducing neonatal mortality.

Conclusions

1. A series of 941 cases of premature delivery was studied. The incidence of prematurity in this clinic was found to be 2.95 per cent.

2. The causes of premature labor and delivery were classified as maternal, fetal, and placental.

3. The obstetric factors in premature deliveries were discussed. The incidence of operative delivery in this group was 27.9 per cent.

4. The gross infantile mortality was 33.3 per cent. The corrected infantile mortality was 18.8 per cent. Both gross and corrected infantile mortality rates have shown a steady decline in the past ten years.

5. It was concluded that the causes of premature delivery are, in many cases, beyond the control of the obstetrician. His role in the prevention of prematurity consists in the control of syphilis and febrile diseases, and continued research on the toxemias of pregnancy.

6. The obstetric management at the time of delivery was found to affect the infantile mortality. It was shown that spontaneous or low forceps deliveries were the procedure of choice. The use of episiotomy was found to be of value. Morphine as an analgesic agent was contraindicated.

7. The availability of prompt oxygen therapy and expert pediatric care is of prime importance to the premature infant.

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ECTOPIC PREGNANCY*

Selected Data From 110 Cases Including a Report of Two Unusual Cases

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EXTRAUTERINE pregnancy is considered one of the most acute emergencies met by the gynecologist. Frequently it may not exhibit itself with classical acuteness, and it then becomes a diagnostic problem of much greater magnitude.

The cases presented in this study are pathologically proved cases of ectopic pregnancy occurring on the Gynecological Service of The Montreal General Hospital over the ten-year period ending October, 1944. Cases with a clinical diagnosis of ectopic pregnancy not substantiated by subsequent pathologic findings have been excluded. With 8,721 admissions and 8,705 operations during the same period the frequency of ectopic pregnancy on this service has been about 1 in 79 cases. This is in agreement with the incidence of 1.3 per cent reported by Wynne,¹ although general statistics state that it occurs about one in every 200 operative gynecologic cases.

The operations on these cases were performed by 14 individual surgeons comprising the attending and resident staffs on the gynecologic service. There were 3 deaths in the series, presenting a gross mortality of 2.72 per cent. Over 20 per cent of the cases were classified as poor risks preoperatively, and an additional 26 per cent were in fair condition.

Age

The age groups of 25 to 30 years, and 30 to 35 years each showed 31 patients (28.1 per cent), the largest number noted in any five-year group. There were 23 patients between the ages of 35 and 40 years, 16 patients between the ages of 20 and 25 years, 3 under the age of 20, and 6 over the age of 40 years. It is seen, therefore, that all but 9 patients were between the ages of 20 and 40 years (91.6 per cent), with 56.2 per cent falling into the 25- to 35-year group. These figures are in general agreement with the usual statistics.

Parity

The occurrence in the relation to parity reveals that 37 patients (33.6 per cent) had never been pregnant before. There were 49 patients (44.5 per cent) who had never had a viable child and 35 patients (31.8 per cent) had only one child. There were only 26 patients (23.5 per cent) who had more than one child. Taking five years without pregnancy or contraception as a basis of relative sterility, there were 53 patients (48 per cent) in this series who had absolute or relative sterility. These findings tend to substantiate the usual stated frequency of ectopic pregnancy in the long-sterile or relatively sterile woman.

Seasonal Influences

In reviewing these cases we were impressed by the relative variation in the number of patients admitted to the service in each individual month of the year. The total admissions

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to the service per month maintain a much more constant level, as our capacity is limited and there is always a large waiting list of patients for admission. It is interesting to speculate on the influence of seasons and climatic changes. Although no definite seasonal cycle was noted in this series, the higher incidence of the condition during the months of May, August, and November agrees in part with the generally recorded fertility curves in this region.

Past History

The past history of lower abdominal laparotomies performed in 34 patients (30.9 per cent) is in keeping with the usual figures, and supports the conclusion that intra-abdominal operative procedures may well be a factor in the etiology of the condition. Curettage had also been done for various reasons on 22 patients, but as this figure corresponds to the general incidence of the operation in our gynecologic service it could not be of conclusive evidence. Previous abortions had occurred in 36 patients (32.7 per cent), and is of unquestionable importance in the etiology of ectopic pregnancy. The question of pre-existent pelvic inflammation is, of course, intimately associated with abortions and operations, and as such cannot be completely estimated. There were, however, 10 patients who had had postpartum or post-abortual sepsis, and 9 patients with definite Neisserian pelvic inflammatory disease, making a total of 17.2 per cent proved cases of infection.

It is of interest to note that two cases of ectopic followed an operation for tubal ligation. Information as to type of procedure used was not available, as both operations had been done in other localities.

One case of ectopic followed subtotal hysterectomy performed in our clinic, and evidently resulted from the since discarded procedure of attaching the medial ends of the tubes and broad ligaments to the cervical stump before final peritonealization.

Recurrent Ectopics

Recurrent ectopic pregnancies occur in about 3.6 per cent of the patients reported (Smith,² Mayo and Strassmann³) in the literature. In our series there were 10 patients (9 per cent) who had had previous ectopic pregnancies, the longest intervening period being twelve years and the shortest, five months. We had two repeat cases of our own. The first occurred five months after the previous ectopic. There had been noted at the first laparotomy an extensive inflammatory lesion of the other tube, but the precarious condition of the patient had precluded further surgical manipulation at that time. The second ectopic pregnancy recurred after one year, and examination of the unaffected tube at the first operation showed no gross abnormality.

Menstrual Cycle

The relationship between the type of menstrual cycle and the occurrence of ectopic pregnancy was not particularly informative, as 95 patients (86.3 per cent) had what could be considered cycles of normal frequency and duration. It was interesting to note that one patient menstruated regularly on a 21-day cycle, which is usually associated with sterility.

Amenorrhea

A history of amenorrhea is considered a valuable diagnostic aid and was present in 77 of our patients (70 per cent); 28 patients had five weeks' amenorrhea, 27 patients had six weeks, 11 patients had seven weeks, 6 had eight weeks, and 5 patients had over eight weeks' amenorrhea. Thirty-three cases (30 per cent) gave no history of amenorrhea, the vaginal bleeding beginning with the regular menstrual period or in the ensuing weeks.

Symptoms

The most outstanding symptom in these patients was lower abdominal pain. It was present in all but one case, which proved to be an unruptured interstitial pregnancy discovered accidentally upon laparotomy. The pain was described as sharp in character and referred to the affected side in 69 patients (62 per cent). It was dull in character and not

localized in either lower quadrant in 34 patients (39 per cent), and it was referred to the unaffected side in 6 patients. Pain in the lower back was present in 30 patients, and pain in the scapular region was noted in 15 patients, all of whom proved to have massive collections of free blood in the abdomen.

Mild feeling of faintness with gradations of severity up to complete syncope was present in 39 patients (35.4 per cent), several of which occurred while the patient was in bed. This is a very valuable aid to diagnosis, as it strongly suggests intra-abdominal bleeding.

Menstrual irregularity either following or without amenorrhea was present in all patients except 12 (10.9 per cent) with dark chocolate-colored vaginal bleeding being noted at some time in 90 patients (81.8 per cent). This latter type of vaginal discharge which is associated with the slow shedding of the uterine decidua has become one of the more valuable symptoms which we use in diagnosis. In 19 patients there was heavy vaginal bleeding simulating abortion, but this usually was a later manifestation.

Nausea and vomiting occurred in association with the pain in 33 patients (30 per cent). The other gastrointestinal symptoms, such as diarrhea, tenesmus, etc., were found in only 6 patients. Bladder symptoms of irritation, frequency, and dysuria were noted in 13 patients (11.8 per cent).

Physical Findings

Temperature and pulse records on admission conform for the most part with the generally accepted picture in these patients. Eleven patients registered subnormal temperatures and 3 patients had temperatures exceeding 100.3° F. The remaining 96 patients had oral temperatures not exceeding 100.3° F., with 80 per cent of the entire series not exceeding 99.3° F. Ninety of the patients (81 per cent) showed increased pulse rates over 80 per minute, with 50 per cent registering rates over 100 per minute. Admission systolic blood pressure readings were not remarkable except for about 25 per cent of cases lying below 100. Rapid falls in systolic pressure when recorded at half-hour intervals proved extremely helpful in diagnosis and early intervention in treatment. This has now become routine in our care of suspected cases.

Signs

Pallor was a noticeable feature on examination in 77 patients (70 per cent). Abdominal tenderness was found in almost all of the patients, it being localized to the affected side in 72 patients. Cullen's sign, present in 2 patients, was a rare accompaniment, as is generally known (Way¹). Pelvic findings showed a soft cervix in 39 patients (35.4 per cent), enlargement of the uterus in 51 (46.3 per cent), brownish vaginal discharge in 81 (73.6 per cent), and a palpable extruterine mass in 103 patients (93.6 per cent). The mass was definitely unilateral in 97 (88.1 per cent) of the patients and, in addition, encroached on the cul-de-sac in 68 (61.8 per cent). Pulsation of the uterine vessels, acute tenderness on movement of the cervix, Chadwick's sign, and patulous cervix were noted, but in a small percentage of patients.

Hematology

Preoperative blood studies were not complete in every case, often because of the obvious diagnosis and the urgency of the condition. Our experience in 85 cases showed a hemoglobin of less than 60 (Sahli) in 38 per cent of the cases and a red blood count of less than 3,000,000 in 23 per cent of the cases. The true blood depletion after a smart hemorrhage failed to show up quickly in these estimations, often taking up to forty-eight hours to become evident through the hemoglobin or red blood count.

Contrary to the generally considered view, leucocytosis may be extremely high in these cases and cannot be taken as an index to pelvic inflammatory disease in the differential diagnosis. The leucocyte counts were elevated above 10,000 in 49 per cent of the cases studied, and in one case rose to 22,000. As has been pointed out by Farrar,⁵ leucocytes are increased in the presence of hemorrhage and no great diagnostic aid was received from these estimations. Sedimentation rates also proved to be more confusing than helpful.

Except for a consistent fall in red blood cell and hemoglobin estimation on repeatedly daily counts as an indicator of progressive blood loss, we have had little assistance in diagnosis from blood studies. They can be used to more advantage as an indication for replacement of the blood by transfusion both preoperatively and postoperatively.

Transfusions

Blood transfusions were given before the operation to 10 patients, and during or after the operation to 53 other patients, 15 receiving more than one transfusion. Thus transfusion was given to 57 per cent of the patients, and accounts in no small way for the reduction of shock in these patients. Forty-one patients (37.3 per cent) showed preoperative shock, while only 13 (11.8 per cent) displayed postoperative evidence of shock.

Location

Although it is usually accepted that either tube may be affected with equal frequency, in our series in 70 patients (63.6 per cent) the ectopic was on the right side, and in 40 patients (36.3 per cent), on the left. At operation 22 patients (20 per cent) were unruptured, although in 4 patients leakage was present through the distal end of the tube. Sixty-seven (60.9 per cent) were demonstrably ruptured, and 21 patients (19 per cent) had partially or completely aborted. It was not always possible to locate the point of original nidation but, from operative and pathologic findings, in 67 cases (60.9 per cent) it was in the ampullar portion of the tube, in 32 cases (29 per cent) in the isthmus, and in 7 cases (6.3 per cent) in the interstitial portion of the tube. The latter is considerably higher than most observers have recorded (Urdan⁶). Of those in the interstitial portion of the tube, 2 were unruptured. In 3 cases the mass was entirely outside the tube; these cases were classified as abdominal, although none was proved primary in that site. One case was not recorded and there were no cases of ovarian pregnancy.

Treatment

Early operative interference, after proper preparation for replacing blood loss has been made, is the treatment of choice. Thirty-six of our patients (32.7 per cent) were operated upon within four hours of admission. Thirty additional patients (27.2 per cent) had received operative treatment within twenty-four hours, and another 15 patients (13.6 per cent) before forty-eight hours had elapsed. In total, 73.5 per cent of the patients were treated within forty-eight hours of admission, while 29 patients had delayed operations, usually because of the obscurity of diagnosis.

The establishment of the most propitious time for operation in some of these cases can demand a nicety of surgical judgment which is exacting. This arises in the differentiation between pure peritoneal shock and the general effects of a hemorrhage which is rapidly increasing. We have seen several cases in which the initial shock at perforation was so profound as to preclude operation until that shock was treated adequately, while the slowly bleeding patient may lose a large quantity of blood into the abdomen before developing the signs of shock due to hemorrhage, and will withstand immediate operative interference much better.

Surgical removal of the affected tube, along with the ovary on the same side, was done in 74 patients (67 per cent). In 34 patients (30 per cent) the ovary was left, and in 2 patients neither the tube nor the ovary was removed. It is imperative that both adnexal areas should be examined at operation. The usual procedure is to control the bleeding from the affected side and then scrutinize the opposite tube and ovary. Although not encountered in this series, bilateral ectopics are reported and should be excluded.

Concomitant Operations

As a general principle, other elective operations are not undertaken at the time of operation for ectopic pregnancy. It has been our opinion that minimal surgical intervention in the presence of hemorrhage, shock, and possible infection is the proper method of dealing with this emergency. Excluding the operation for suspension of the uterus, which was done in 45

cases and which is often indicated to prevent the uterus becoming adherent posteriorly, 44 other operations were done in this series. On analysis, 19 of these operations were indicated and 25 were elective. Two of the patients who died were among those classified as the elective group, but otherwise the morbidity and duration of hospitalization was not materially different from the entire series.

Diagnostic curettage was performed in 13 patients (11.8 per cent). The procedure is far from being diagnostic although the finding of decidua without chorionic villi is suggestive of ectopic. As pointed out by Te Linde,⁷ decidua-like changes in the endometrium are sometimes seen in the absence of pregnancy, and one's interpretation of such a finding should be guarded.

Siddall and Jarvis,⁸ and others have pointed out that the duration and amount of vaginal blood loss are the factors which are responsible for the presence or absence of decidua on curettage. The sooner curettage is done after the bleeding begins, the more likely one is to find decidua. There is a point in the course of the condition when a "dry scrape" results which should likewise be highly suggestive of ectopic as the decidua may be completely shed and the necessary stimulation for regeneration is absent because the products of conception still maintain their activity. Later in the old or missed ectopic the findings of premenstrual or interval endometrium may be positively misleading, as has been our experience. Therefore, curettage is only of absolute value when chorionic villi are found, as it shows the presence of an intrauterine pregnancy.

Diagnostic colpotomy was performed in 10 cases. Free blood was found in 8 patients with the fetus being delivered through the colpotomy wound in one of these patients. The value of this procedure is only in differentiating collections of pus and blood. There is no excuse for using it to differentiate between two such conditions as ovarian cyst and ectopic, in which laparotomy is indicated in both. A negative needling or colpotomy does not exclude ectopic, and in our series of 10 patients, 7 had a very stormy postoperative course, which we felt was partially due to the introduction of infection into such a fertile field for growth. If this procedure is done routinely in every case, it will undoubtedly confirm the diagnosis in a high percentage of cases, but the introduction of infection into an otherwise clean case outweighs the value of a procedure which is usually not necessary.

Friedman and Aschheim-Zondek tests were carried out so infrequently in this series that no conclusions can be drawn from the findings.

Postoperative Course

Of the entire series 84 patients (76.3 per cent) had a smooth uncomplicated convalescence. Twenty-six patients (23.7 per cent), as judged by protracted periods of fever, shock, and definite complications and morbidity, were recorded as having stormy postoperative courses. Nine patients (8.1 per cent) showed chest complications, such as pneumonia, bronchitis, atelectasis, and tuberculosis. Nine patients (8.1 per cent) had wound infections with one case of dissolution of the wound. Eight patients had urinary tract infections, while 4 patients developed postoperative ileus and 4 patients had peritonitis, 3 of the latter comprising our mortality. The average postoperative stay in hospital was 15.1 days.

Pathology

The pathologic findings reported decidua-like reaction in the tube of 81 patients (73 per cent), with chorionic villi in various stages of activity in 96 patients (87 per cent). Associated pelvic inflammation, acute, chronic, or tuberculous, was present in 22 patients (20 per cent), and other pathologic findings such as fibroids, ovarian and parovarian cysts, endometriosis, hydro- and hematosalpinx, were present in 27 patients (24.5 per cent).

Mortality

There were three deaths in the series for a mortality of 2.72 per cent. These deaths occurred on the third, fifth, and twelfth postoperative days, two being from generalized peritonitis, and the other from shock and peritonitis.

The first was a patient, 40 years of age, who was admitted for a plastic repair with a history of menstrual irregularity for three years. During the course of the repair under general anesthesia, the patient's general condition rapidly deteriorated and a laparotomy was done at once. The abdomen contained over 1,000 c.c. of blood, and a ruptured isthmie pregnancy close to the uterus was found. Subtotal hysterectomy and salpingo-oophorectomy was done and transfusion given as soon as possible. There was of necessity some delay as it was before the days of blood banks, and her blood group had not been typed preoperatively. She died on the fifth day of generalized peritonitis.

The second patient died of postoperative shock and anemia. She had been admitted sixteen hours before operation to the medical ward with a high fever and a history of diarrhea, nausea, and vomiting. During the day her condition became rapidly worse, with a fall in blood pressure and signs of intraperitoneal fluid. At operation, a ruptured ectopic pregnancy was found, and the tube and ovary removed. In spite of three transfusions she never recovered from shock and died on the third postoperative day.

The other death was due to generalized peritonitis, ileus, dissolution of the wound, and terminal pneumonia on the twelfth day. Both tubes and one ovary were removed at operation and the uterus was suspended. At operation there was extensive evidence of a pre-existing bilateral pelvic inflammation. The postoperative course was extremely stormy with paralytic ileus and distention developing and, finally, dissolution of the wound. Salpingectomy of the unaffected side in this case was classified as an elective operation in spite of the inflammatory lesion, in a sense justifying its removal.

Thus, two fatalities resulted in patients subjected to operative procedures in excess of the truly necessary lifesaving measures, in one case purely by accident but in the other in an effort to save a second laparotomy at a later date. It is, indeed, in our experience, much better to treat only the primary condition when dealing with extrauterine pregnancy.

It is of interest to note that we have had no deaths in the past seven years which have seen the establishment of the blood bank and the increasing use of sulfonamides. Of the two factors the blood bank is probably more important, as rapid replacement of blood and the administration of serum for shock are lifesaving.

Case Reports

CASE 1.—Ectopic tubal pregnancy following subtotal hysterectomy.

Mrs. M. K., aged 36 years, was admitted to The Montreal General Hospital on Aug. 16, 1936. The menstrual history was relatively normal. She had been married at the age of 22 years and at 25 years had had a normal full-term child. Six years later she had been treated for a spontaneous three months' abortion in this hospital. At that time a fibroid was felt in the uterus. For the next four months she had had frequent, irregular, profuse, and prolonged periods, which resulted in a general decline in the patient's health. On April 18, 1931, she was readmitted to hospital, transfused, and five days later had a supraecervical hysterectomy performed for a degenerated, necrotic, infected leiomyoma. The adnexa were normal and were not removed. She made an uneventful recovery and was perfectly well until the readmission in 1936.

Complaints on this admission were vaginal bleeding and brownish discharge intermittently for three weeks, associated with dull aching pain in the right lower quadrant and loin during the same period.

On examination the patient appeared somewhat pale. The pulse was 96 per minute, fair volume; the temperature was 98.2° F., and the blood pressure 117/70. The chest was clear. The abdomen was rounded, inclined to flabbiness, with a lower abdominal midline scar. Deep abdominal palpation in the suprapubic region elicited a moderate degree of tenderness. Pelvic examination showed a cystic mass bulging into the cul-de-sac with elicited crepitations suggesting a collection of blood.

Laparotomy was performed under general anesthesia. Numerous adhesions covered the pelvic basin. On freeing these, a large hemorrhagic mass about the size of a clenched fist was elevated from the region of the right adnexa. This was removed and the abdomen closed in layers without drainage. The left tube and ovary appeared normal.

Pathologic Report.—"Sections show fragments of Fallopian tube and ovary embedded in blood clot which is partially organizing. In one section several edematous chorionic villi are seen in the clot and in the adjacent fixed tissue there is a decidual reaction. No fetus is seen."

Diagnosis.—Ectopic tubal pregnancy.

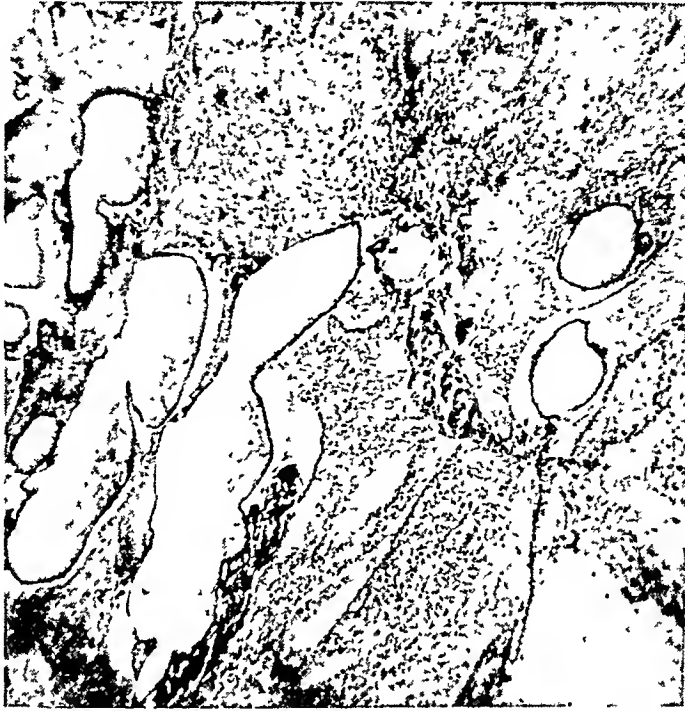


Fig. 1.—Case 1.—Mrs. M. K. Ectopic pregnancy after supracervical hysterectomy. Section of Fallopian tube showing placental tissue.

CASE 2.—Ectopic pregnancy in a tuberculous Fallopian tube.

Mrs. J. S., aged 28 years, was admitted to The Montical General Hospital, on Feb. 8, 1937, with complaints of pain in the lower abdomen, amenorrhea of two months, faintness, loss of strength, and pain in the abdomen on deep breathing. Menstrual history was normal. She was married at the age of 26 years and had had no pregnancies or abortions. The last normal period was December 5, and early in January she had experienced morning nausea. On January 15 she had developed a sharp pain in the left lower quadrant which lasted a few hours and subsided, leaving moderate soreness in the abdomen, associated with dysuria and pain in the rectum on defecation. Subsequently she had two similar attacks of pain, the last occurring on the day of admission and being very severe, with associated fainting.

On admission she appeared pale, and evidently was in severe abdominal pain. Examination revealed a weak pulse, 100 per minute, with a blood pressure of 85/65. Abdominally there was some fullness in the lower abdomen with definite tenderness in the left lower quadrant. Blood count showed: red cells, 2,500,000; hemoglobin, 46 per cent; white cells, 12,000. Urinalysis was negative. A diagnosis of ruptured tubal pregnancy was made.

Two hours after admission the abdomen was opened under cyclopropane anesthesia. On opening the abdomen, fresh blood under pressure gushed out. A ruptured ectopic pregnancy was found in the left tube with the fetus lying in the blood clot. The tube was removed without the ovary. The right tube was palpated and nothing abnormal was noted although the tube was not examined visually. No effort was made to clear the abdomen of clots as the patient's condition was precarious. Transfusion was given on the table and the immediate condition was fair. Twenty-four hours after operation the temperature rose to 101.2° F., and it remained at that level for twenty days. Blood transfusion was given on three occasions, 1,500 c.c. in all. In spite of all treatment, the postoperative course was extremely stormy, with chills, fever, and marked distention.

Nine days postoperatively the pathologist reported: "Specimen consists of left Fallopian tube 9 cm. in length and the fetus 3.5 cm. in length. Sections show two conditions—blood clot, chorionic villi, and decidual reaction in the Fallopian tube. There is also extensive tuberculosis involving the mucosa of the tube."

Diagnosis.—Ectopic tubal pregnancy, with coexistent tuberculosis of the Fallopian tube.



Fig. 2.—Case 2.—Mrs. J. S. Ectopic pregnancy in a tuberculous Fallopian tube. Section of the tube showing chorionic villi and two tubercles.

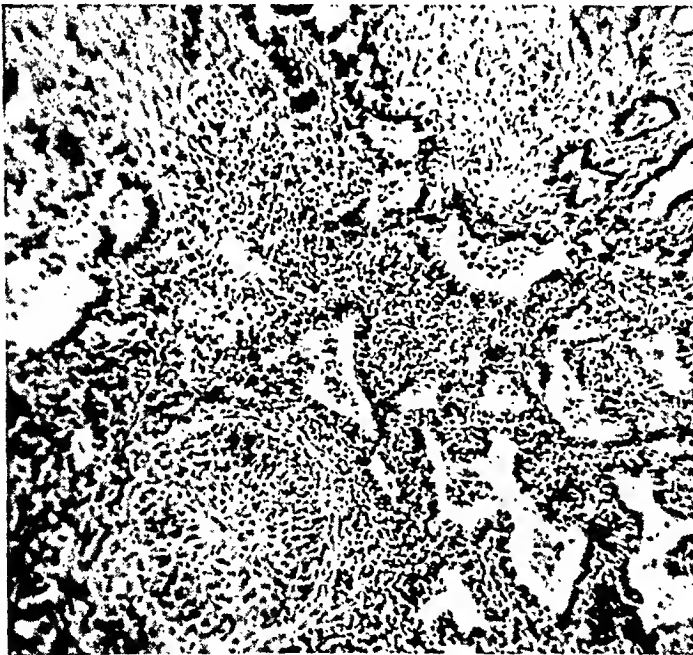


Fig. 3.—Case 2.—Mrs. J. S. Fallopian tube mucosa showing chronic inflammation and tubercle (lower left).

TABLE I. HOSPITALS GROUPED ACCORDING TO NUMBER OF BIRTHS DURING 1944

HOSPITALS	CHICAGO		REST OF COOK COUNTY		TOTAL FOR COOK COUNTY		TOTAL FOR ILLINOIS	
	NUMBER OF		NUMBER OF		NUMBER OF		NUMBER OF	
	HOSP.	BIRTHS	HOSP.	BIRTHS	HOSP.	BIRTHS	HOSP.	BIRTHS
With less than 50 births	2	47			2	47	21	577
With 50 to 149 births	5	471	4	380	9	851	36	3,549
With 150 to 349 births	9	2,309			9	2,309	61	14,844
With 350 to 499 births	5	2,030			5	2,030	22	8,937
With 500 to 999 births	21	16,475	5	3,581	26	20,056	63	45,809
With 1000 or more births	22	35,878	5	8,652	27	44,530	33	53,158
Total	64	57,210	14	12,613	78	69,823	236	126,874
Per cent	27.1	45.0	5.9	10.0	33.0	55.0		

TABLE II. STATISTICAL DATA FOR HOSPITALS IN COOK COUNTY GROUPED IN BIRTH CLASSES

CLINICAL ACTIVITY	LESS THAN 50 BIRTHS (2)		50-149 BIRTHS (9)		150-349 BIRTHS (9)		350-499 BIRTHS (5)		500-999 BIRTHS (26)		1000 OR MORE B. (27)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
<i>I. Mothers</i>												
General												
1. Delivered in hosp.	45		840		2284		2008		19854		44048	
a. Spontaneous	42	93.3	737	87.7	1799	78.8	1437	71.6	13843	69.7	30611	69.5
b. Operative	3	6.7	103	12.3	485	21.2	571	28.4	6011	30.3	13437	30.5
2. Abortions	1		14		20		41		551		1476	
3. Ectopic pregnancies			4		2		8		38		143	
Complications			48	5.7	163	7.1	143	7.1	1738	8.8	4506	10.2
1. Infection			39	4.6	75	3.3	64	3.2	776	3.9	2082	4.7
2. Toxemia			3	0.4	43	1.9	19	0.9	558	2.8	1365	3.1
3. Hemorrhage			5	0.6	44	1.9	60	3.0	389	2.0	1016	2.3
4. Other			1	0.1	1				15	0.1	43	0.1
Operative procedures			107	12.8	533	23.3	646	32.0	6543	33.0	15313	34.7
1. For deliv. of infant	3	6.7	103	12.3	485	21.2	571	28.4	6011	30.3	13437	30.5
a. Forceps	2	4.4	89	10.6	409	17.9	494	24.6	4938	24.9	10866	24.7
(1) Low	2	4.4	77	9.2	382	16.7	459	22.9	4604	23.2	10088	22.9
(2) Mid			6	0.7	25	1.1	24	1.2	315	1.6	665	1.5
(3) High			6	0.7	2	0.1	11	0.5	19	0.1	113	0.3
b. Cesarean section	1	2.2	7	0.8	42	1.8	63	3.1	736	3.7	1643	3.7
(1) Low cervical					26	1.1	24	1.2	387	1.9	1097	2.5
(2) Classical	1	2.2	7	0.8	15	0.7	37	1.8	320	1.6	487	1.1
(3) Porro					1		2	0.1	29	0.1	59	0.1
c. Breech extract.			6	0.7	25	1.1	11	0.5	256	1.3	728	1.7
d. Version & extract.					6	0.3	3	0.2	64	0.3	152	0.3
e. Destructive			1	0.1	3	0.1			17	0.1	48	0.1
2. For other purposes			4	0.5	48	2.1	75	3.6	532	2.7	1876	4.2
a. Mechanical induct.					8	0.4	8	0.4	35	0.2	124	0.3
b. Removal of plac.					5	0.2	39	1.9	113	0.6	221	0.5
c. Uterine packing			1	0.1	7	0.3	1		81	0.4	194	0.4
d. Transfusion			3	0.4	28	1.2	27	1.3	303	1.5	1337	3.0
<i>II. Infants</i>												
1. Born in hospital	47		851		2309		2030		20056		44530	
Live births	47	100.0	826	97.1	2250	97.4	1984	97.7	19675	98.1	43619	98.0
2. Premature births	2		35	4.1	81	3.5	77	3.8	895	4.5	1633	3.7
3. Injured in birth			4	0.5	7	0.3	7	0.3	46	0.2	118	0.3
<i>III. Mortality*</i>												
1. Stillbirths			25	29.4	59	25.6	46	22.7	381	19.0	911	20.5
2. Neonatal deaths			13	15.3	30	13.0	35	17.2	317	15.8	1006	22.6
3. Maternal deaths			2	2.4	3	1.3	6	3.0	32	1.6	76	1.7

*Per 1,000 births.

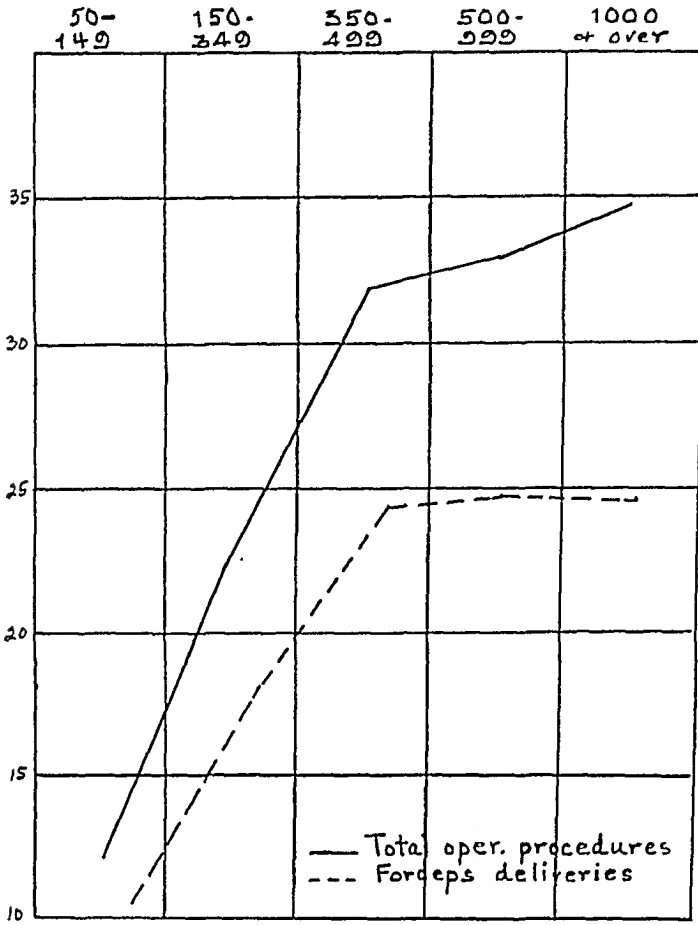


Fig. 1.—Per cent of operative procedures by birth classes in Cook County, 1944.

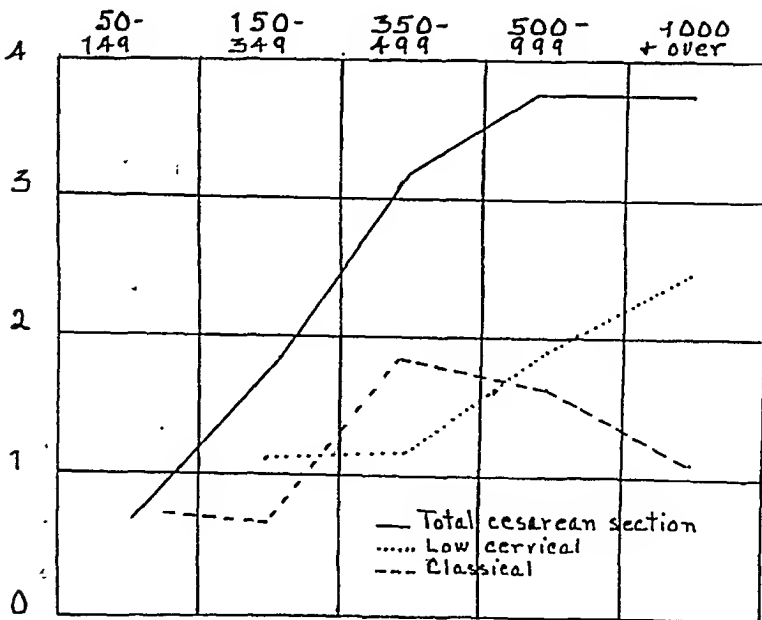


Fig. 2.—Per cent of cesarean section by birth classes in Cook County, 1944.

ward trend, from 2.4 to 1.7, and from 29.4 to 20.5, respectively, while the neonatal losses per 1,000 births tend to grow higher as the number of births increase, from 15.3 to 22.6 (Fig. 4).

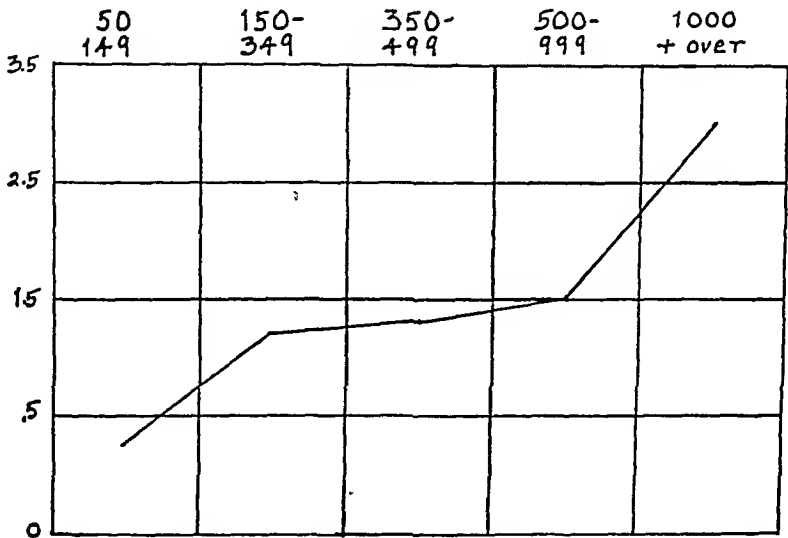


Fig. 3.—Per cent of transfusions by birth classes in Cook County, 1944.

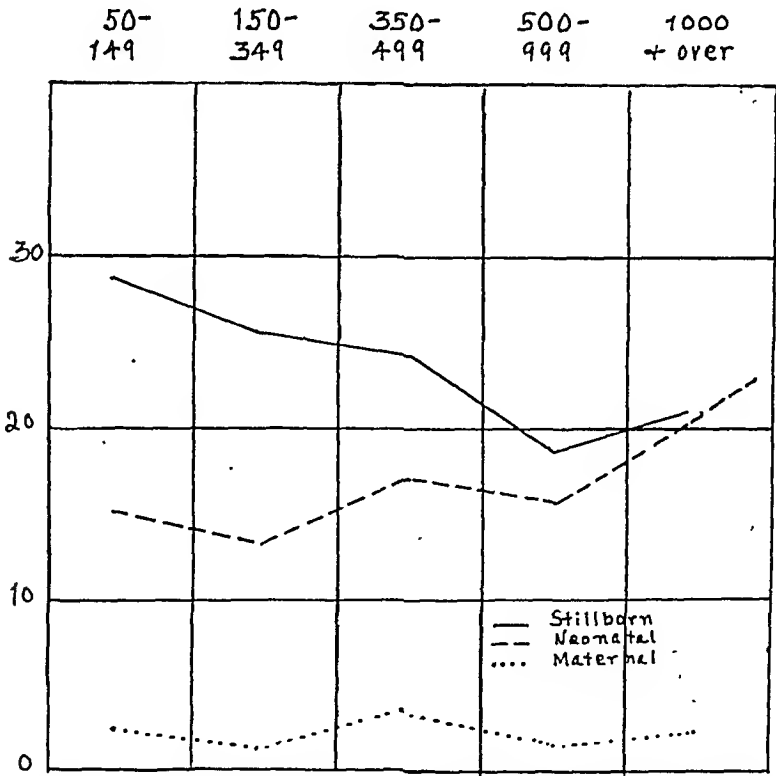


Fig. 4.—Mortality rates per 1,000 births by birth classes in Cook County, 1944.

Variations in procedures and in mortality rates in the individual hospital are striking: spontaneous deliveries range from 14.1 per cent to 99.2 per cent; operative cases, from 0.8 per cent to 85.9 per cent; cesarean sections, from 0.6 per cent to 10.0 per cent. The averages for all the hospitals in the county are:

70.2 per cent, 29.8 per cent, and 3.6 per cent, respectively. The ratio of births by cesarean section to the total number of operative deliveries in the county is 12.1 per cent; in the individual hospital it reaches from 1.4 per cent to 33.6 per cent (Fig. 5). The mortality rate of mothers per 1,000 births ranges from 0.0 (31 hospitals with 16,350 births) to 14.5 (one mother in 69 deliveries), for live born infants from 0.0 to 31.7 (9 neonatal deaths in 284 babies), and the stillbirth rate ranges from 3.7 to 41.5 (14 stillbirths in 337 babies). The averages for the county are 1.7, 20.1, and 20.4, respectively (Fig. 6).

Table III was prepared for the purpose of comparing the data as they apply to the hospitals in Chicago, those in the rest of the county, both of these groups as a unit, and all of the hospitals in the State.

As is to be expected from the large number of births in Cook County, the percentages for the County approach closely those given for similar data in

TABLE III. STATISTICAL DATA FOR HOSPITALS IN CHICAGO, REST OF COOK COUNTY, ALL OF THE COUNTY, AND IN ILLINOIS

CLINICAL ACTIVITY	CHICAGO HOSPITALS		REST OF COOK COUNTY		TOTAL FOR COOK COUNTY		ALL HOSPITALS IN ILLINOIS	
	(64)		(14)		(78)		(236)	
	NO.	%	NO.	%	NO.	%	NO.	%
<i>I. Mothers</i>								
A. General								
1. Delivered in hospital	56609		12470		69079		125534	
a. Spontaneous	39820	70.3	8649	69.4	48469	70.2	91065	72.5
b. Operative	16789	29.7	3821	30.6	20610	29.8	34469	27.5
2. Abortions	1451	1:39	652	1:19	2103	1:33	4386	1:28
3. Ectopic pregnancies	149	1:380	46	1:271	195	1:354	398	1:317
B. Complications	5686	10.0	912	7.3	6598	9.5	11408	9.1
1. Infection	2570	4.5	466	3.7	3036	4.4	5683	4.5
2. Toxemia	1745	3.1	243	1.9	1988	2.9	2944	2.3
3. Hemorrhage	1326	2.3	188	1.5	1514	2.2	2674	2.1
4. Other	45	0.1	15	0.1	60	0.1	107	0.1
C. Operative procedures	18994	33.6	4151	33.3	23145	33.5	38410	30.6
1. For deliv. of infant	16789	29.7	3821	30.6	20610	29.8	34469	27.5
a. Forceps	13777	24.3	3021	24.2	16798	24.3	27404	21.8
(1) Low	12825	22.7	2787	22.4	15612	22.6	24698	19.7
(2) Mid	828	1.5	207	1.6	1035	1.5	2219	1.8
(3) High	124	0.2	27	0.2	151	0.2	487	0.4
b. Cesarean section	2107	3.7	385	3.1	2492	3.6	4332	3.5
(1) Low cervical	1326	2.3	208	1.7	1534	2.2	2082	1.7
(2) Classical	694	1.2	173	1.4	867	1.3	2131	1.7
(3) Porro	87	0.2	4		91	0.1	119	0.1
c. Breech extraction	654	1.2	372	3.0	1026	1.5	2166	1.7
d. Version & extract.	186	0.3	39	0.3	225	0.3	484	0.4
e. Destructive	65	0.1	4		69	0.1	83	0.07
2. For other purposes	2205	3.9	330	2.7	2535	3.7	3941	3.1
a. Mechanical induc.	155	0.3	20	0.2	175	0.3	383	0.3
b. Removal of placenta	304	0.5	74	0.6	378	0.5	535	0.4
c. Uterine packing	192	0.3	92	0.7	284	0.4	674	0.5
d. Transfusion	1554	2.7	144	1.2	1698	2.5	2349	1.9
<i>II. Infants</i>								
1. Born in hospital	57210		12613		69823		126874	
Live births	56007	97.9	12394	98.3	68401	98.0	124342	98.0
2. Premature births	2088	3.6	635	5.0	2723	3.9	5394	4.3
3. Injured in birth	164	0.3	18	0.1	182	0.3	298	0.2
<i>III. Mortality*</i>								
1. Stillbirths	1203	21.9	219	17.4	1422	20.4	2532	20.0
2. Neonatal deaths	1174	20.5	227	18.0	1401	20.1	2654	20.9
3. Maternal deaths	98	1.7	21	1.7	119	1.7	227	1.8

*Per 1,000 births.

the State. Differences are noted in the figures of the Chicago hospitals as compared with the hospitals in the rest of the County, particularly in the higher reported incidence of complications, the preference for the low cervical over the classical cesarean section, and the more frequent use of transfusions

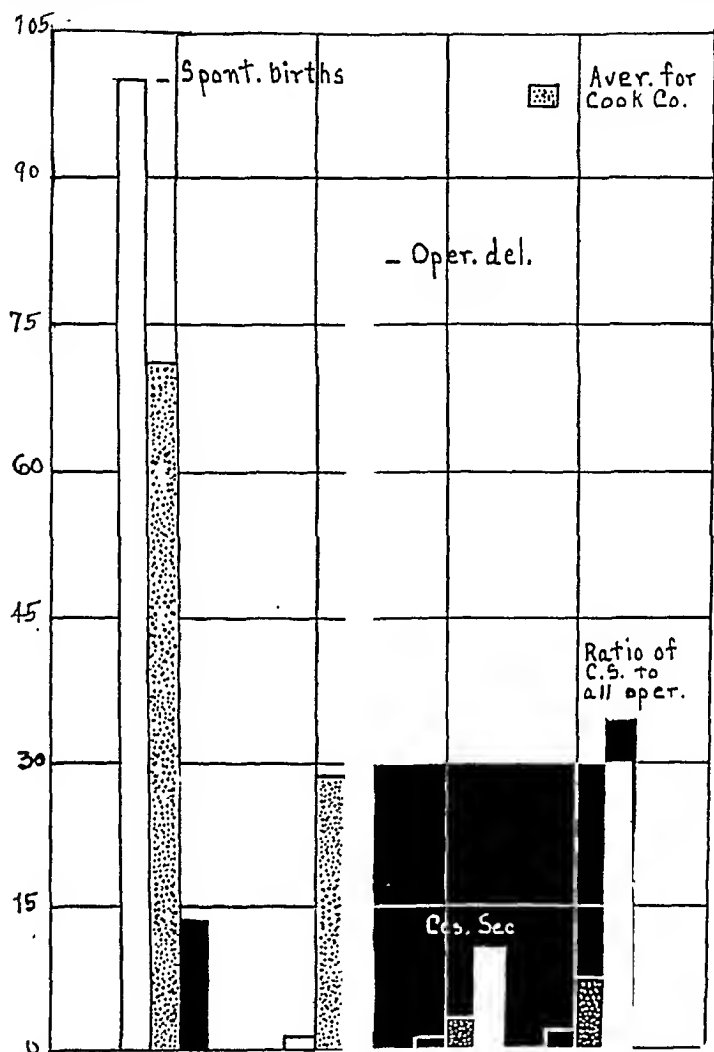


Fig. 5.—Range in obstetric procedures in individual hospitals in Cook County, 1944.

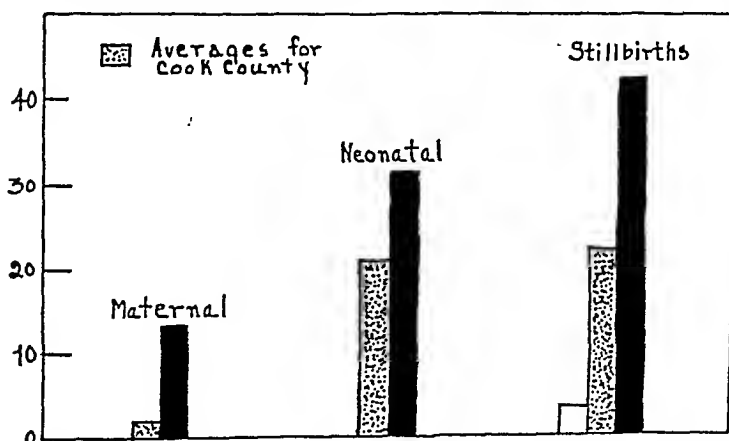


Fig. 6.—Range in mortality rates per 1000 births in individual hospitals in Cook County, 1944.

in Chicago. An interesting observation is that in Chicago one abortion is reported for every 39 deliveries, and one ectopic pregnancy for every 380 deliveries, while in the hospitals in the rest of the county, the figures are one in 19, and one in 271, respectively.

Each of the three principal complicating hazards was subdivided: the 4.4 per cent of infections or morbidities were classed as genital in 2.5 per cent; as extragenital, in 0.9 per cent; as due to both genital and extragenital causes, in 0.2 per cent; and of undetermined etiology, in 0.8 per cent. The 2.9 per cent toxemic patients were grouped as pre-eclampsia in 1.8 per cent; as eclampsia, in 0.2 per cent; and other toxemias, in 0.9 per cent. Of the 2.2 per cent of women who had hemorrhage, 0.6 per cent had antepartum bleeding, 1.3 per cent postpartum bleeding, and 0.3 per cent had hemorrhage both before and after labor.

Consideration of maternal and infant losses formed an important part of this study. Hospitals in Cook County had a favorable rank among hospitals of other counties of the State, with rates per 1,000 births of 20.4 for stillbirths, 20.1 for neonatal deaths, and 1.7 for maternal deaths; the corresponding rates for all the hospitals in the State were: 20.0, 20.9, and 1.8. A visualization of these losses by the hospitals of the State and the comparative ranking of the 74 counties is afforded by the maps in Figs. 7, 8, and 9.

Maternal deaths, as reported by the hospitals, were checked with the records of the Division of Vital Statistics. Deaths shown only by the Division were referred to the hospital for further inquiry. Twenty-six Chicago hospitals, with 14,673 deliveries, and 5 other hospitals in Cook County with 1,677 deliveries, making a total of 16,350 births, had no maternal deaths. The number of births in individual hospitals of this group of 31 institutions ranged up to 1,985.

An analysis of the causes of maternal mortality and their frequency for hospitals in Chicago, Cook County, and the State is shown in Table IV.

TABLE IV. CAUSES OF MATERNAL DEATHS, AND THEIR FREQUENCY, IN ILLINOIS HOSPITALS DURING 1944

INTERN. LIST NO.	CAUSE	CHICAGO	REST OF COUNTY	TOTAL OF COOK COUNTY		ALL HOSPITALS IN ILLINOIS	
				NO.	PER CENT	NO.	PER CENT
140-141	Abortion	21	5	26	21.9	44	19.4
142	Ectopic	7	2	9	7.6	17	7.5
143-146	Hemorrhage	13	2	15	12.6	37	16.3
144-148	Toxemia	17	4	21	17.6	38	16.7
147	Infection	22	6	28	23.5	55	24.2
145-149	Other Dis.	13	2	15	12.6	29	12.8
150	Unspecified	5	—	5	4.2	7	3.1
	Totals	98	21	119	100.0	227	100.0

It is noted that in this State, infection leads all other causes, being responsible for 24.2 per cent of all maternal deaths; toxemia and hemorrhage are nearly equal in importance, with 16.7 per cent and 16.3 per cent, respectively.

Although this presentation is concerned with the obstetric activities in the hospitals of Cook County, it should be of interest to the members of this

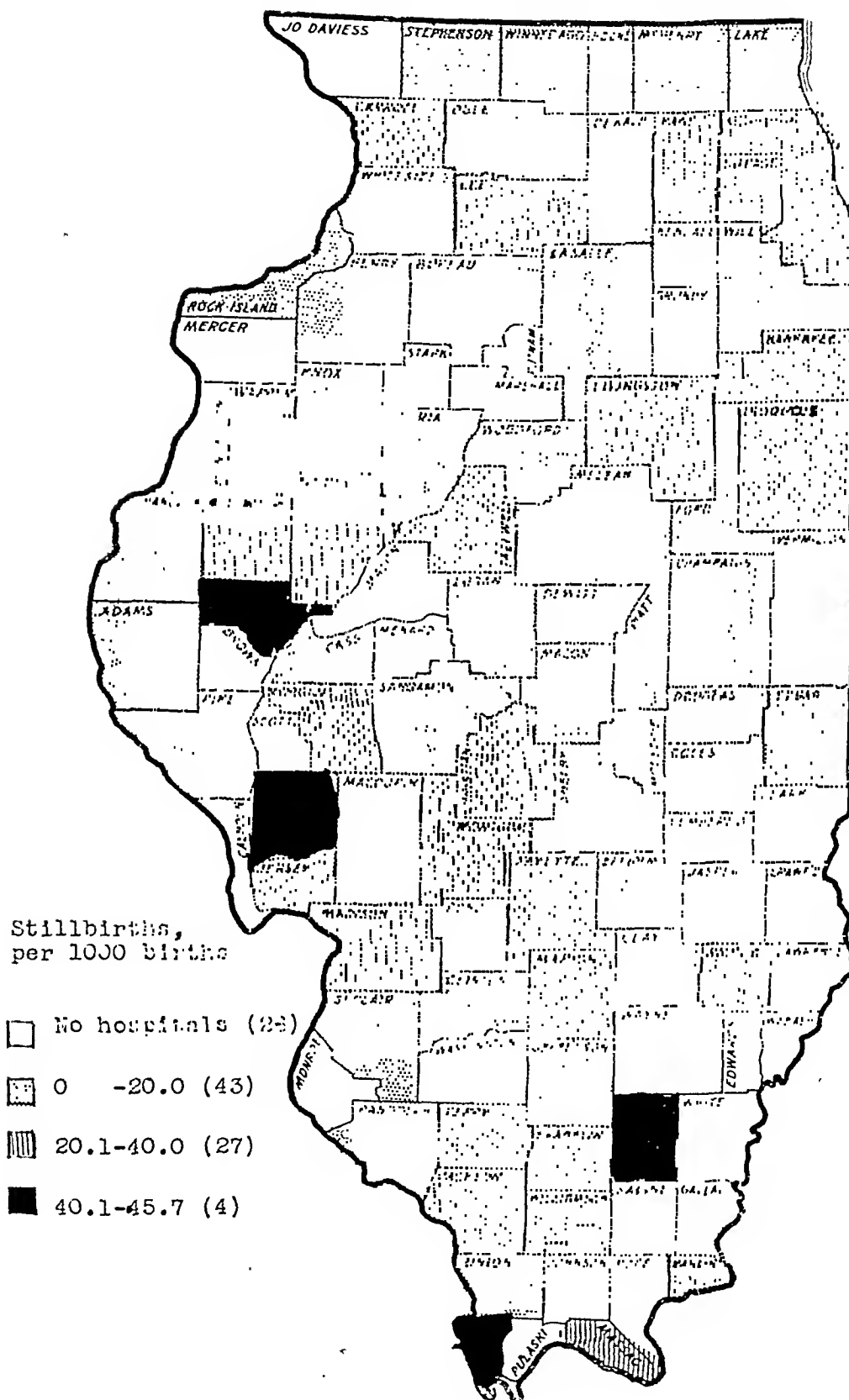


Fig. 7.—Stillbirth rate in hospitals of each county of Illinois, 1944. Counties in black, reading down, are: Schuyler, Greene, Hamilton, Alexandria.

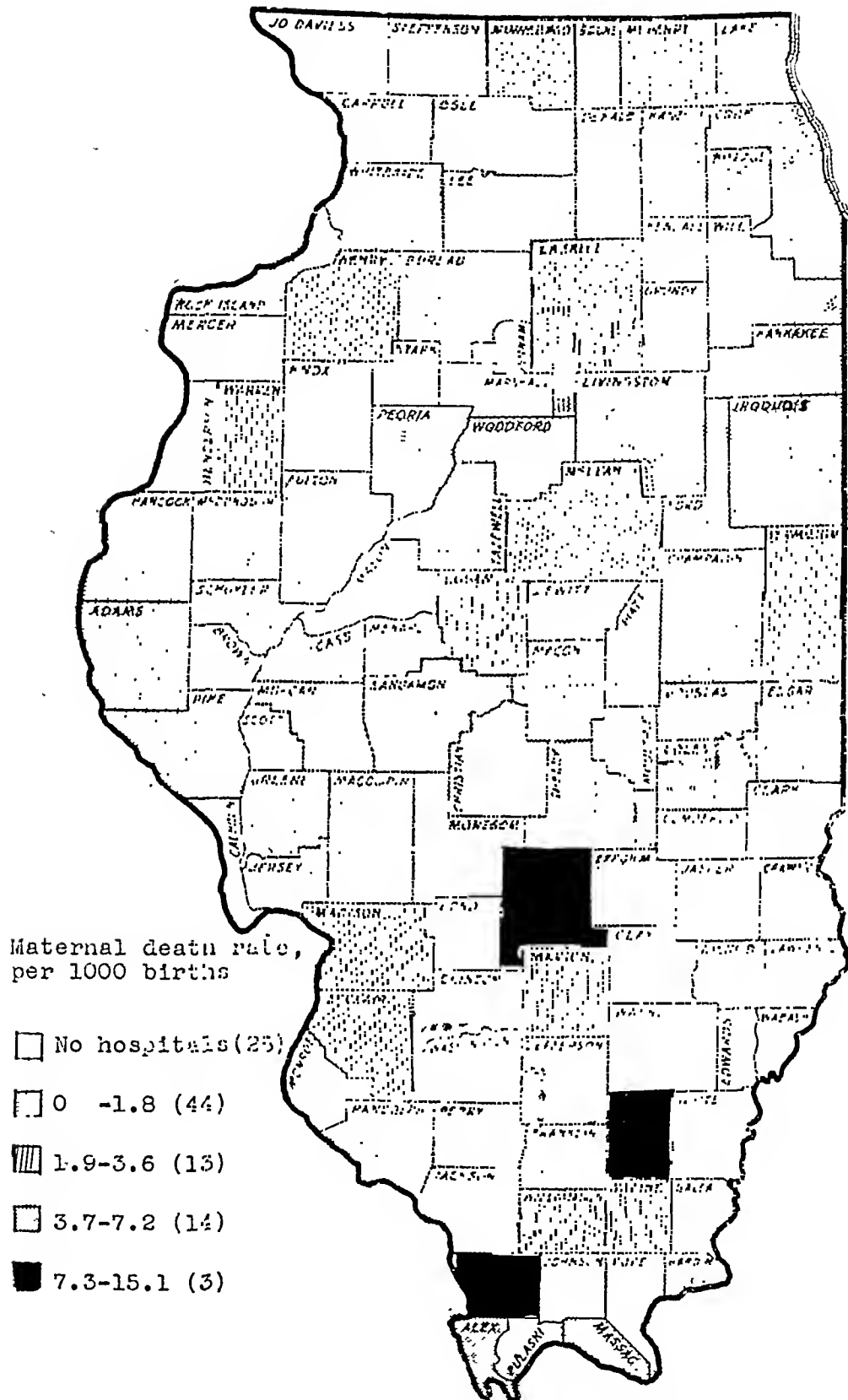


Fig. 9.—Maternal mortality rate in hospitals of each county of Illinois, 1944. Counties in black, reading down, are: Fayette, Hamilton, Union.

TABLE V. COMPARATIVE DATA FOR HOSPITAL AND HOME DELIVERIES IN ILLINOIS DURING 1944

	BIRTHS		STILLBIRTHS		NEONATAL DEATHS		MATERNAL DEATHS	
	NO.	PER CENT	NO.	RATE PER 1,000	NO.	RATE PER 1,000	NO.	RATE PER 1,000
Hospital deliveries	126,874	90.3	2,532	20.0	2,654	20.9	227	1.79
Home deliveries*	13,686	9.7	518	37.8	367	26.8	22	1.61
Total for State	140,560	100.0	3,050	21.7	3,021	21.5	249	1.77

*Of this number, 337 mothers were delivered by midwives, or 0.24 per cent of the total number cared for in the state.

Society to record briefly the salient data of the total obstetric facts in the State for 1944. Table V shows that 90.3 per cent of all births in Illinois during 1944 occurred in hospitals, that 9.7 per cent were home deliveries, and that 0.24 per cent were attended by midwives. It is also noted that home deliveries had a higher stillbirth and neonatal death rate than deliveries cared for in hospitals.

Summary

By means of tables, graphs, and maps, there is presented a statistical analysis of the obstetric activities in hospitals of Cook County during 1944. The study has three main headings: mothers, infants, and mortality.

It is shown that of the 69,079 mothers cared for, 70.2 per cent had spontaneous deliveries; among the 29.8 per cent of those who had operative intervention for the birth of the infant, there were 24.3 per cent forceps cases, 3.6 per cent cesarean sections, 1.5 per cent breech extractions, 0.3 per cent version and extractions, and 0.1 per cent craniotomies.

In addition to these 29.8 per cent receiving aid in delivery, another 3.7 per cent of mothers required operative procedures for other purposes, such as mechanical induction of labor in 0.3 per cent, manual removal of the placenta in 0.5 per cent, uterine packing in 0.4 per cent, and transfusion in 2.5 per cent. Disregarding the very small number of women who may have had more than one operative procedure, it is noted that one-third of all mothers had some type of intervention during the birth process.

Of all mothers whose pregnancies ended at term or prematurely, 9.5 per cent had some form of obstetric complication: 4.4 per cent had infection, 2.9 per cent had toxemia, and 2.2 per cent had hemorrhage. Another 0.1 per cent had nonobstetric complications involving the various organs of the body. In addition to these mothers, 9.6 per cent of all who were delivered, there were recorded 2,298 other women as obstetric casualties; 2,103 who aborted, and 195 who required surgical treatment for ectopic gestation.

Of the 69,823 infants delivered, 98.0 per cent were born alive, 3.9 per cent were premature births, and 0.3 per cent were injured during the birth episode.

In noting the mortality on the basis of each 1,000 births, there were 20.4 stillbirths, 20.1 neonatal deaths, and 1.7 maternal losses. Of the 119 maternal deaths in Cook County during 1944, puerperal infection ranked first in cause with 23.5 per cent, toxemia was second with 17.6 per cent, and hemorrhage

was third with 12.6 per cent; abortion with or without sepsis accounted for 21.9 per cent of all deaths, ectopic gestation for 7.6 per cent, and a variety of other diseases for 16.8 per cent.

It is believed that critical examination by the profession of the information presented, and in particular, the study by each hospital staff of the report sent by the Division of Maternal and Child Hygiene of its own obstetric work, with comparative data for its birth class and for the State, should lead to improvement in trends of obstetric practice, to lowering unduly high operative rates in some institutions, to less frequent resort to cesarean sections in others, to more ready use of blood or plasma for prophylaxis or for treatment, and to the general leveling off of the peaks, and extremes, and marked variations in procedures. The consequence of such changes should reflect itself in a further reduction of mortality rates, making childbirth safer for the mother and her newborn infant.

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Discussion

DR. FREDERICK H. FALLS.—Necessarily, a discussion of a paper of this kind must deal with an analysis of the figures as presented. An attempt would have to be made to point out the significance of the figures rather than to dispute or agree with the figures themselves. They are a fixed proposition. One of the most interesting things is to know that there are 28 counties in the State of Illinois where women cannot go into a hospital to have a baby. I think, therefore, those of us who are teaching obstetrics have to recognize that it is necessary to teach a man to go into a home, boil up a kettle of water on the kitchen stove, and, if necessary, do a forceps with some lay person holding the leg, as well as teaching advanced obstetrics in institutions with all the modern conveniences.

I think it is interesting to see that our men in the smaller hospitals are more conservative in their management of obstetric cases, and that that conservatism offsets some of the disadvantages, because the mortality rate appears to be about the same in all institutions. When one has all the facilities, one is inclined to do more operating, and, even if the operator is skillful, it will be seen that unnecessary operating may result in increased maternal mortality and morbidity. It should be noted that cesarean section results are just about as good in small hospitals as big ones. It is obvious that in the smaller institutions they do not realize the value of packing the uterus, since in larger hospitals they pack in a higher percentage of cases, while in the smaller hospitals in only a small percentage was the uterus packed. We think that the value of this should be taught more frequently to our undergraduates.

The statistics emphasize the frequency of ectopic pregnancy.

Complications.—9.1 per cent of these cases were complicated cases. You can see that infection, hemorrhage, and toxemia account for 9.0 per cent, and all the other complications amount to only 0.1 per cent, which shows where we should direct our teaching. Hemorrhage, infection, and toxemia are the big causes of maternal mortality. We should emphasize the diagnosis and treatment of these conditions in our undergraduate teaching.

Cesarean section.—I think we as obstetricians in Illinois could be pretty well satisfied with the results—3.5 per cent is a reasonable figure. When we go into some hospitals that have 14 per cent, it shows what can happen when physicians are allowed to run wild. We are pretty sound as a group when we keep our rate down to 3.5 per cent. The fact that the low cervical and the classical are practically the same in the group as a whole (1.7 and 1.7) is interesting, and that only in 0.1 per cent was it necessary to do a Porro.

Destructive operations were done in 0.07 per cent. I think no one in obstetric practice questions the value of doing a destructive operation at the proper time and under proper conditions.

The maternal deaths are about what one would expect, puerperal sepsis leading, with toxemia and hemorrhage about the same.

The final thing that I wish to point out is the mortality in abortions, 21.9 per cent. That is the mortality rate that is checked up against the obstetrician when, in most cases, he is not at all responsible.

DR. J. P. GREENHILL.—The records studied by Dr. Newberger show that more than 90 per cent of the women delivered in the State of Illinois during 1944 had their babies in hospitals, and less than 10 per cent had home deliveries. In spite of the fact that the vast majority of the babies were delivered by general practitioners, even in Cook County, almost one-third of the women had operative deliveries. The incidence of forceps deliveries is not high for specialists and for institutions where specialists in obstetrics are trained, but it is excessive for general practitioners. Likewise, an incidence of 10 per cent for cesarean section is about twice what it is in the leading maternity hospitals of this country. Any hospital with such a high frequency of cesarean section should carefully review its cases. Undoubtedly, the institutionalizing of patients and the availability of general anesthesia accounts for the high incidence of operative deliveries.

The records which were available to Dr. Newberger proved what has been repeated over and over again, namely, that the chief causes of death of puerperal women are: infection, toxemia, and hemorrhage, and in the order stated. In Dr. Newberger's analysis of the deaths in the Cook County Hospitals during 1944, 23.5 per cent of all the maternal deaths were due to infection, 17.6 per cent to toxemia, and 12.6 per cent to hemorrhage. However, in my opinion, these figures do not present a true picture. I believe that far more deaths are due to hemorrhage than are listed on the monthly reports or on death certificates. In Dr. Newberger's statistics, for example, we find that transfusions were given in 2.5 per cent of all the cases. These transfusions undoubtedly were not limited to the group of women whose deaths were listed under the heading of hemorrhage; but many transfusions were given to women whose cause of death was listed as infection, toxemia, or other conditions, but who, nevertheless, lost a sufficient amount of blood to require transfusion. Likewise, abortion was responsible for 21.9 per cent of all the deaths in the Cook County group, and surely a large proportion of these deaths were directly or indirectly due to loss of blood. Furthermore, ectopic pregnancy was given as the cause of death of 7.6 per cent of all the cases, and certainly in these cases hemorrhage was an important factor in the loss of life. Even in cases of infection and toxemia, there is frequently considerable loss of blood which plays an important role in the failure of recovery. C. A. Gordon has shown that, for a number of years, hemorrhage has been the most important cause of maternal death in Brooklyn. In fact, in 1943, hemorrhage was a significant factor in 53.6 per cent of all puerperal deaths in Brooklyn. This information was not obtained from monthly reports or death certificates but from careful study of the original hospital records and personal interviews with the physicians in charge of the women who died. If fatality reports were properly filled out and in detail, we would most likely find that hemorrhage is the most important cause of death, not only in Brooklyn, but also all over the United States.

In view of the importance of hemorrhage as a cause of maternal death, it behooves all of us to heed this fact, because undue loss of blood is, to a large extent, preventable. It is true that Yerushalmy's study does not bear this out. This author (*The Child* 7: 110, 1943) analyzed the maternal mortality statistics of the United States for 1941 and 1942. He found that in 1942 there was a 10 per cent reduction in the deaths due to infection, an 11 per cent reduction in the deaths from toxemia, but practically no decrease in the number of deaths from hemorrhage. This gloomy picture can certainly be changed by routine blood studies during pregnancy, blood typing and determination of the Rh factor, hospitalization of every woman who bleeds during pregnancy whether it is early or late in gestation, emptying of the uterus from below or above for hemorrhage due to placenta previa and abruptio placentae, proper conduct of the second stage, and, above all, conservative management of the third stage of labor. The saving of blood will not only reduce

the number of deaths which are directly due to hemorrhage, but also it will enable puerperal women to combat complications such as infection and toxemia which might otherwise prove fatal. When blood is lost, it should be replaced as soon as possible and in sufficiently large amounts. In urgent cases, two, and even three veins should be used at the same time. Blood is still the puerperal woman's most powerful ally.

DR. ROBERT M. GRIER.—I am very pleased with the progress made in reducing maternal mortality in our city. Only ten years ago I reviewed the maternal mortality for ten of the central states. At that time the maternal mortality was as high as 0.45 per cent. In the well run maternities in this city it was only 0.22 per cent. Now, for the whole city, this figure is down to 0.18 per cent.

In our study, deaths from infection accounted for 45 per cent for the states as a whole; whereas, in these previously mentioned Chicago hospitals it was only 15 per cent. Naturally, if the deaths from infection are reduced, there will be an apparent increase in percentage in many of the other causes, such as toxemia and hemorrhage. It is in this one category that most of our improvement has been made. It might appear from this report that deaths from the hemorrhage are actually on the increase, which of course is not true.

DR. JOSEPH L. BAER.—Some years ago, this Society sponsored an investigation of maternal mortality in the Chicago area. The study was carried out for three years and reported to the Society. Since then an analysis of deaths has been carried out by the Maternal Welfare Committee of Chicago and, more particularly, by the Sub-committee on Maternal Mortality. Our figures will be analyzed shortly, but I am certain that all the members present will agree with me that the figures will show that hemorrhage is far and away the No. 1 cause of maternal death in the Chicago area.

The maternal mortality committee learned to look with disfavor on the frequency with which only glucose and sera are given to mothers. I want to call attention to the fact that plasma is available in all hospitals of Chicago and blood in many of them, particularly in those with their own blood banks. There is also now available resuspended red cells in volume equivalent liter for liter to whole blood. These resuspended red cells can be obtained on application to the Samuel Deutsch Serum Center of the Michael Reese Hospital. In the near future there may be a distribution center at the City Health Department. In the month of April twenty hospitals availed themselves of this service. These resuspended red cells are immediately available in this twenty-four hour service. I am sure it will mean a big step forward if all hospitals in the city could have this type of service. One frequent error in judgment is stopping with only one transfusion of 500 c.c. Unfortunately, too many men think when they have given one transfusion they have done their duty by the patient who might require four or five times that much.

DR. A. J. KOBAK.—There are three questions that I would like to raise and discuss. First of all, neonatal deaths seem to be higher in the larger hospitals of the city of Chicago. Premature babies born in smaller hospitals, however, are usually sent to the larger hospitals because they do not have the standard facilities for care. I wonder, therefore, to what extent premature babies dying in the larger hospitals increase the deaths in these institutions, and at the same time decrease the deaths in the smaller hospitals.

The second question is regarding cesarean section. It seems to me that most of the sections we have at Cook County Hospital are repeat sections. I believe this is true for many of our larger hospitals. To what extent do such cases swell the figures for cesarean section in the larger institutions?

Finally, in the analysis made by Dr. Newberger, it appears that in the larger hospitals where higher standards in obstetrics are found, a greater number of operative interferences were noted. Many obstetricians routinely employ outlet prophylactic forceps. In their hands, this procedure preceded by an episiotomy gives best results. If outlet forceps or low forceps deliveries were excluded, how would the operative interference compare, would it then be less in the larger hospitals or equal to that found in the smaller hospitals?

DR. W. C. DANFORTH.—I want to speak about the incidence of operative delivery. I think our teaching should be toward conservatism. The hospital group I represent has a high rate of operative deliveries, the great majority being outlet forceps. Versions and extractions, and more difficult forceps are rarely done. Outlet forceps in skilled hands is a very safe procedure and does not increase mortality at all. That may be emphasized because, in a sixteen-year period, we have maintained an average maternal mortality of 0.12 per cent. In teaching institutions, I think that the operative deliveries are largely restricted to outlet forceps. This operation does not increase mortality.

As to cesarean section, over the same period of time I mentioned a moment ago, the incidence of cesarean section was 3.7 per cent, with a mortality of 0.89 per cent. I think last year when figures were presented from the University of Chicago they varied from ours by a few tenths per cent.

I want to emphasize one other thing, that in case of bleeding, if drug therapy does not suffice immediately, packing should be carried out. Valuable as transfusion is, it is still more valuable to have the woman keep her own blood in circulation than to put in some one else's blood. As soon as hemorrhage becomes persistent after administration of ergotrate, then we should pack.

DR. NEWBERGER (Closing).—As to the comment that in Chicago hemorrhage seems to be the leading cause of death, it is not fair to compare the analysis that the Committee, of which Dr. Baer is the Chairman, is making with the figures from the reports sent into the State Health Department. The Cook County Maternal Welfare Committee is doing a creditable job by going thoroughly into each maternal death after investigation by a trained obstetrician. Our figures are based entirely upon reports from institutions, and when these reports state that sepsis is the leading cause it has to be so accepted.

In answer to Dr. Kobak's question, this presentation aimed to give the obstetric data for the County as a whole and for the city as a whole rather than for the individual hospitals. It is quite true if we studied the facts for Cook County Hospital we would find a different situation. The same is true when we consider the Sarah Morris Hospital of Michael Reese, to which many premature babies born outside are brought. Naturally in these two institutions the neonatal death rate is increased. The same thing applies with reference to the question of operative procedure. When one makes an analysis of this kind one must classify forceps deliveries as operative labors.

STUDIES OF THE ORIGIN AND TREATMENT OF RECURRENT TRICHOMONAS VAGINITIS*

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RECURRENT trichomonas vaginitis remains one of the most difficult therapeutic problems in pelvic infection. In the mass of investigative work, little positive evidence has been presented as to the manner in which the organism first gains admission to the body, and the method of its extension to other organs. Considerable evidence has shown that the urinary tract and the prostate are frequently foci of extension or even entrance; questionable evidence suggest the upper genital tract as a focus. Basic zoological studies establishing the separate identity of *Trichomonas vaginalis*, *Trichomonas buccalis*, and *Trichomonas hominis* are not in accord with our clinical impression that attacks of diarrhea are frequently followed by the reappearance of trichomonads in the vagina. This work has been undertaken in a further attempt to clarify these problems and to improve the methods of treatment.

History

The literature reveals increasing evidence differentiating vaginal and intestinal species of trichomonads. Lyneh¹ (1922) felt that the oral, vaginal, and intestinal species were morphologically similar, although he cited the five flagellar intestinal type (*Pentatrichomonas ardin delteili*), suggesting that it might be a distinct species. Kofoed and Swezy² (1929) reported a study of *P. ardin delteili*, suggesting its individual identity. Andrews³ (1929), after a study of *T. vaginalis* from culture using a Giemsa stain, stated that it is morphologically identical to *T. hominis*. Powell⁴ suggests that her conclusion was based on "study of individual organisms which had undergone autotomy, and which were therefore small and had undulating membranes running the length of their bodies." Bishop⁵ (1931), in her report on the division of trichomonads, includes drawings indicating specific morphologic differences between *T. vaginalis* and *T. hominis*. These are full-length undulating membranes with a trailing flagellum not found in *T. vaginalis*. Bland, Goldstein, and Wenrich⁶ (1931) concluded that the oral, intestinal, and vaginal trichomonads are separate species. They admitted confusion over the type of intestinal organisms, stating that further work was required to differentiate *P. ardin delteili* and *T. hominis*. They described a third intestinal trichomonad with three flagella, previously reported by Cleveland⁷ and Westphal⁸ (1935), and stated that *T. vaginalis* and *T. hominis* are separate species because of the presence of a full-length undulating membrane with a free posterior flagellum in *T. hominis* not found in *T. vaginalis*. Powell⁴ (1936) after careful study, differentiated *T. vaginalis* and *T. hominis* on the basis of difference in (1) size, (2) number of granules in the blepharoplast, (3) presence or absence of a parabasal apparatus, (4) length of the undulating membrane, (5) presence or absence of a trailing flagellum, (6) length of the chromatine basal rod, (7) nuclear characteristics, (8) presence or absence of a karyosome, (9) presence or absence of cytoplasmic granules. Liston⁹ (1940) studied *P. ardin delteili* with Leishman's staining method. Kirby¹⁰

*Presented before a meeting of the Chicago Gynecological Society, Dec. 15, 1944.

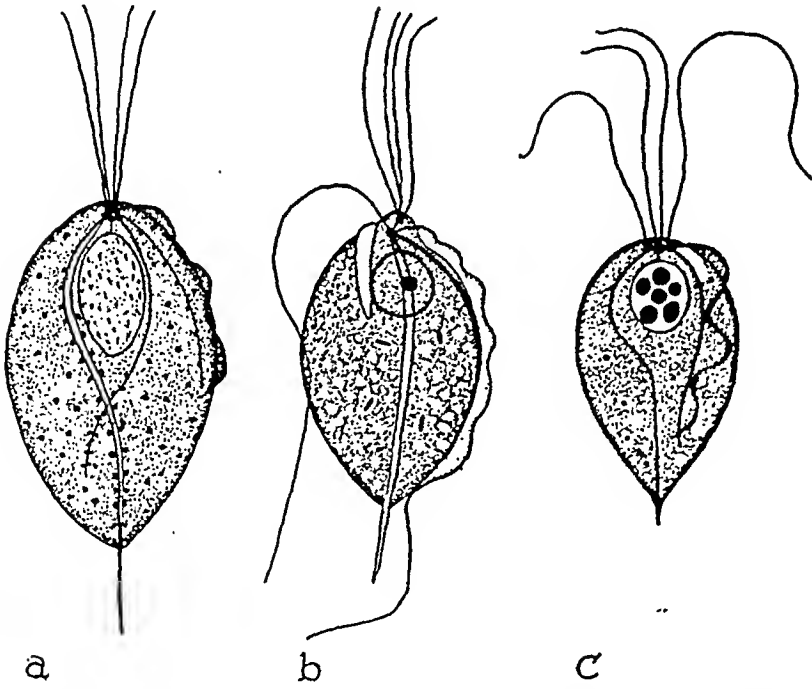


Fig. 1.—a, *Trichomonas vaginalis*; b, *Trichomonas hominis*; c, *Trichomonas buccalis*.

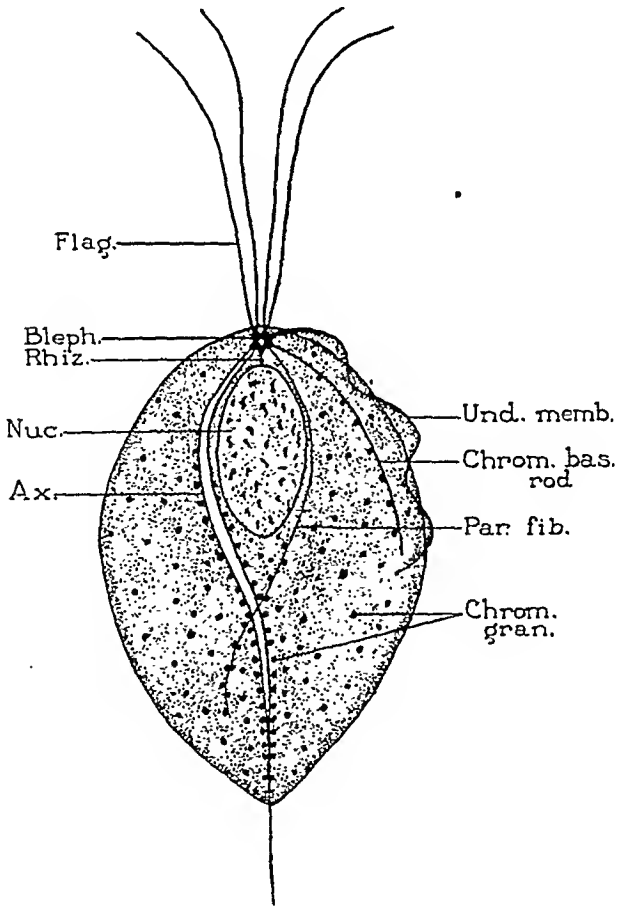


Fig. 2.—*Trichomonas vaginalis*

(1943) reported a study of *P. ardin delteili* (he suggests *Pentatrichomonas hominis* as more correct nomenclature), expressing his conviction that it is a distinct species. He used dark-field examination and a silver and gold stain, and stated that "differences in flagellar organization should be considered indicative of differentiation of groups of trichomonads. . . ." He believes that the independent fifth anterior flagellum of *Pentatrichomonas* serves to distinguish it from *T. hominis*.

In solving the problem of specie differentiation, physiologic studies are helpful. Working with bacteria-free cultures, Kupferberg¹¹ (1940) reported that the optimal pH for the growth of *T. vaginalis* is 5.4 to 5.5 Adler¹² (1942), working with bacteria free cultures of *T. hominis*, reported that the optimal pH is 6.6 to 7.2.

Westphal⁸ (1935) attempted to alter the morphologic characteristics of *T. vaginalis* by altering the serum content of his culture media. The size varied, but the general morphologic picture remained constant. He noted small trichomonads, with full-length undulating membranes without a posterior flagellum similar to these described by Andrews, but explained them on the basis of autotomy.

Transplantation experiments have been attempted on kittens, monkeys, and human subjects. Bonestell¹³ (1936) reported 73 per cent success in attempts to establish *T. hominis* in the intestinal tracts of kittens. *T. vaginalis* and *T. buccalis* could not be so established. Hegner¹⁴ (1934) reported that *T. hominis* in the intestine of man can maintain itself for twenty days in the vaginal tracts of Rhesus monkeys. There was no evidence of multiplication. Dobell¹⁵ (1934) reported successful establishment of *T. hominis* in the vagina of one Rhesus monkey. Kessel and Gafford¹⁶ (1940) were unable successfully to transplant *T. hominis* into the vaginal tracts of six Rhesus monkeys, but they were able to establish a growth of *T. vaginalis* in three of sixteen attempts. Stabler, Feo, and Rakoff¹⁷ (1941) were unable to establish *T. hominis* in the vaginal tracts of fifty women. Many successful transplantations of *T. vaginalis* have been made in human vaginas, using infected vaginal secretions and cultures.

Personal Observations

In an attempt to rule out the intestinal tract as a possible source of infection or reinfection of the vagina with *Trichomonas*, a series of 39 treatment-resistant cases were studied. These patients were examined through the proctoscope and vaginal smears and cultures also taken. To avoid the possibility of vaginal contamination, specimens of stool were obtained through the proctoscope with a sterile spoon. An attempt was made to avoid contact between lubricants and fecal material, since lubricants often render *Trichomonas* immotile. No enema or laxative was used. No *T. hominis* was found (cultural technique described by Craig¹⁸ used).

The following parasites were demonstrated, however: *Chilomastix mesnili*, *Embadamonas intestinalis*, cysts of *Embadamonas intestinalis*, and cysts of *Endamoeba nana*.

The mucous membrane of the rectum was examined for visual changes which, when present, were seen in an area on the anterior wall approximately 7 cm. above the anus, contiguous to the posterior fornix of the vagina. These changes consisted of redness, swelling, dilated veins, granulation, or pinpoint ulceration. As far as we could determine, there was no correlation between the severity or duration of the vaginal infection and the extent of the lesions seen through the proctoscope. We cannot be sure whether or not there is any relationship between the lesions in the rectal mucous membrane and the vagina infestation with *T. vaginalis*; however, they occurred with such regularity in the same area of the rectum that it seemed too frequent to be mere coincidence.

Six other cases which had positive stool cultures for *T. hominis* were examined vaginally. In no case was *T. vaginalis* found in the vaginal secretion. One case with intestinal trichomonads was followed for ten months, but the vaginal smear remained negative.

There are confused reports concerning the invasion of *T. vaginalis* above the cervix. Hees¹⁰ reported the recovery of trichomonads from ovarian cysts, chronic inflamed tubes, endometrium, placental tissue, and from a five-month fetus removed by cesarean section. Pattyson²⁰ failed to recover trichomonads from the endocervical canal and uterine in fifty cases.

We have been unable to demonstrate any ascension of the trichomonads above the external os of the cervix. We have examined material from the surgical specimens removed from twenty-eight patients with active trichomoniasis. The material was obtained within a few minutes after operation. It was examined in saline suspension, cultured (technique described by Trussel and Plass²¹), and stained (Leishman's stain described by Liston⁹). The material was taken from the uterine canal, tubes, ovarian cysts, pelvic and ovarian abscesses, and amniotic fluid. No trichomonads could be demonstrated.

TABLE I. DIAGNOSIS OF 28 SURGICAL CASES WITH ACTIVE TRICHOMONAS VAGINITIS

Bilateral salpingitis	10
Fibromyoma	15
Ovarian abscess	6
Pelvic abscess	1
Ovarian cyst	11
Pregnancy, 1 month	1
Double uterus	1

TABLE II. MATERIAL FROM SURGICAL CASES EXAMINED FOR *T. VAGINALIS*

Uterine canal	17
Fallopian tubes	17
Ovarian cyst fluid	11
Material from abscess	7
Amniotic fluid	1

However, it is our feeling that elective surgery should not be undertaken in the presence of an active vaginitis of any type. Morbidity is increased in those patients upon whom operative procedures are undertaken in the presence of a vaginitis. It is our distinct impression from clinical experience that either the specific organisms or their symbiotic bacteria are a common cause of pelvic infection, either at the menstrual time or following invasion of the uterine canal. Many workers have demonstrated subepithelial vaginal invasion with abscess formation.¹⁶ Bacteria that cause abscess formation must be pathogenic for the individual.

We have carried on the treatment of this series of patients in a similar manner to those described in our previously reported studies.²² The pH of the vaginal jelly has been varied from time to time, but has been standardized at a pH of 4.0. A few patients complained of burning and smarting during the initial applications, but have soon become accustomed to it without further discomfort. The pH seems to be most efficacious for the control of trichomoni-

asis. In 26 cases of this series we have added the nightly insertion into the vagina of a tablet, a desiccated culture of lactobacilli as reported by Brady and Reid.²³ This has been in an attempt, not only to increase the acidity of the vagina, but also to establish a permanent growth of lactic acid-producing bacilli in the vaginal secretion. When we have been able to accomplish and maintain this normal status, most patients have rapidly recovered and remained well (18 of 26). In this connection we have noticed that in some cases soon after lactobacillus therapy has been started, *Monilia* has appeared in the vaginal secretion (5 of 26). Yeast leads to an increase in acidity of the vaginal discharge, and with it a beneficial effect in eliminating trichomonads. Contraverting this observation we not infrequently found *T. vaginalis* and *Monilia* occurring spontaneously together in the vaginal secretion. We have raised the question and expect to explore the possibility at the earliest opportunity whether the salutary effect of the *Monilia* is produced by an increase in acidity or possibly by products of the growth of the fungus in the vaginal canal.

Method of Treatment

Our plan of treatment for this series has consisted mainly of the following routine: nightly insertion of a tablet of lactobacilli; a morning cleansing douche consisting of 1 dram of lactic acid to 2 quarts of warm water, followed by the instillation of one applicator full of jelly for daytime use. The lactic acid douche and the lactobacilli tablets have been replaced by $\frac{1}{2}$ dram of tincture of iodine in 2 quarts of warm water and topical applications of 1 per cent aqueous solution of gentian violet for the treatment of moniliasis. The jelly has been much more effective in our hands for the treatment of yeast infections than for trichomoniasis (71 cured in a total of 87). However, 62 of 166 patients were cured by the use of jelly and douches alone. The continuance of treatment throughout the menstrual period is essential for cure in both trichomonas and yeast vaginitis. We believe that the addition of lactobacilli tablets will materially increase the number of permanent cures.

If reinfection occurs following three months of gradually decreasing therapy, an immediate search is begun for secondary foci of infection. Since the bladder, in our experience, has been the most frequent demonstrable focus (21 per cent of 234 cases), catheterization is done and repeated several times to prove the presence or absence of trichomonads. The last 3 or 4 c.c. of the specimen is collected in a sterile centrifuge tube, centrifuged at low speed for a minute, and examined immediately. Cystoscopy has been frequently a part of this procedure. If *Trichomonas* is found, or, in its apparent absence, the petechial bullous edema of the urethra or trigone is present, the bladder and urethra are treated biweekly by installations of 5 per cent argyrol or 5 per cent sodium sulfathiazole. We have occasionally added sulfathiazole by mouth in 30-grain doses in an attempt to reduce the coecal flora accompanying *Trichomonas* infestation of the urinary tract.

If the investigation of the urinary tract did not bear fruit, the male partner was examined by the urologist. In several instances, motile trichomonads were found in the prostatic fluid. We still feel that *T. vaginalis* is probably one of

the most important etiological factors in chronic prostatitis. We were only able to cure some of our most resistant cases of trichomonas vaginitis after the husbands had received adequate treatment in the form of massage, prostatic heat, and instillations into the urethra and bladder.

Summary and Conclusions

1. A brief résumé of important literature dealing with specie differentiation of *Trichomonas vaginitis* is presented.
2. A proctoscopic examination of 33 patients with treatment-resistant *Trichomonas vaginitis* was done, with cultures of the material thus obtained. No trichomonads were found in the bowel cultures.
3. Certain visual changes were observed in the rectal mucous membrane of a large percentage of these patients.
4. Six cases with *T. hominis intestinalis* infestations were found to have no vaginal trichomoniasis.
5. Immediate examination of surgical specimens removed from twenty-eight patients with active *Trichomonas vaginitis* revealed no organisms in direct smear or culture.
6. The treatment of *Trichomonas* and yeast vaginitis is described.

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Discussion

DR. FREDERICK FALLS.—We have found that *Trichomonas vaginalis* infestation has frequently been associated with the Holman streptococcus and have felt that this organism rather than the *Tr. vaginalis* does the damage. Dr. Hibbert, working in my clinic, found that in many cases the *Trichomonas* could be eliminated but the streptococcus would survive, and that the symptoms would persist as long as the streptococcus could be found. He then took the streptococcus in pure culture and introduced it into the vagina of a young woman who did not have *Trichomonas vaginitis*, and reproduced the picture of *T. vaginalis* vaginitis without trichomonads.

In some cases we believe that bacteriophage put into the vagina on a tampon seems to help in reducing the rate of growth of these streptococci and that both streptococci and *Trichomonas* disappear from the vagina. In other cases, Dr. Hibbert was not able to produce this effect. By making a vaccine and raising the immunity of the individual to the streptococcus, some of these refractory cases were cured. In some cases the *Trichomonas* and streptococcus were the cause of the lesions, and in other cases the *Trichomonas* acted as a harmless parasite, but with streptococcus in symbiosis would produce the disease.

We have had the same experience as Dr. Allen and Dr. Butler in finding the bladder residual infection after having cleared up the *Trichomonas* infestation.

In younger patients I have used the old method described by DeLee when this infestation was first treated here in Chicago in 1919, in which the vagina was washed out by sodium bicarbonate and bichloride of mercury first, then packed with sodium bicarbonate and with glycerin. This was done in the hospital under anesthetic. For the average case in multiparous women we have used the following routine: scrubbing out the vagina with soap and water, and then putting in 10 per cent silver nitrate, and having them use floraquin suppositories in addition to this local treatment and a formalin douche. In our hands this method has produced very good results. The use of a vaccine in those cases in which the patient's resistance seems to be low and which do not clear up by other methods, has been carried out.

DR. CHARLES E. GALLOWAY.—*Trichomonas* is apparently on the increase. My recent experience with it has been in the Army. In the Army it causes considerable trouble with women who are marching and especially in hot weather. Although it was the Army's policy to keep everyone possible on duty, we realized that women with this disease had to have hospitalization.

Many of us have believed that this disease originated from the rectum. We have taught women certain methods of personal hygiene to avoid it. The present study pretty well rules out any condition in the rectum as a cause. In the 33 cases that were proctoscoped they found no trichomonads in the rectum. Also, in six cases where they found *T. hominis* in the rectum, there were no trichomonas found in the vagina.

It is very interesting to note also that in 28 operated cases no trichomonads were found above the cervix. That also is a fact that ought to be better established.

I would like to know what the authors think of vitamin A in the treatment of *Trichomonas* infestation. They recommend lactic acid douche and lactic acid jelly. The acid douche and jelly are very good, but they should not be carried on too long. I have had some patients tell me confidentially that lactic acid jelly and douches desensitized the whole area.

The bladder should be treated in all resistant cases. I can testify from personal experience that trichomonads can be found in the bladder. I have used Cinquarsone and instilled it in the bladder in resistant cases.

The pH of the vagina is important, but I think you can find trichomonads with a pH of 4 or 5. The pH determination is significant because there is something back of the low pH, something back of the decreased lactic acid in the vagina, something that allows the trichomonads to invade. I get the impression that this may be a psychological change in some cases. Certain classes of women appear more apt to have *Trichomonas* infections than others. Wives with various complexes will furnish more cases of *Trichomonas* infection than women with a normal sexual life.

DR. J. P. GREENHILL.—I was particularly interested in Dr. Galloway's remark that there has been an increase in the incidence of trichomonas vaginitis, but I disagree with this statement. I think the reason we are finding more cases is that we are looking for them. Dr. DeLee deserves credit for having called the attention of American physicians to this condition in 1919. Only two case reports preceded his, one by Dock and the other by N. S. Davis, both published in 1896.

In 1928 I read a paper on this subject before this Society and since then an enormous number of papers have been published on *Trichomonas vaginalis* vaginitis. In spite of this there is no unanimity as far as treatment is concerned. We can cure all cases temporarily,

regardless of the type of therapy. However, in a few weeks or a few months there are recurrences in many cases with every kind of treatment. For some reason or other, some women continue to have recurrences, particularly those who are high-strung, even after every possible source of infection has been treated.

DR. H. CLOSE HESSELTINE.—The essentials of the treatment of *Trichomonas* fall under two headings: one is the cure of the local condition in the vagina, and the other is the prevention of reinfection. The first contention would explain why so many different preparations have given improvement and have caused some patients to remain well, particularly when it is a first or mild infection. The second phase is the crux of tonight's paper.

The number of drugs which Drs. Allen and Butler used is too large to discuss. When one classifies the drugs into pharmacologic headings, they fall into drying or desiccating, coagulating, acidifying or alkalizing, carbohydrate replacements, and other agents. Particularly enough, many preparations which have been used will have as good result if the vehicles alone are employed. Kaolin powder and plain gelatin and glycerin suppositories produce good results. Studies are now in progress on tampons with and without stovarsol. We have treated 16 patients with plain tampons (without stovarsol) and 17 with stovarsol tampons. The results showed little difference. It is extremely important from a scientific point of view that, whenever we try out a remedy, we have a proper and adequate control.

Not only the urinary tract but the cervix is important. Dr. Curtis and subsequently Dr. Gardner have pointed out the persistence of infection in the cervix. Sometimes a persistent trichomonas infection will be cured only when the cervix is put into healthy condition.

Dr. W. W. Scott of the Urologic Department of the University of Chicago has made urethroscopic and cystoscopic examinations on some patients with chronic trichomoniasis. When lesions such as a granular urethritis or a vesical lesion have been eliminated, the vaginal condition, as a rule, has been easier to cure.

As careful and thorough investigators as Drs. Allen and Butler are, it is still possible that they missed finding trichomonads in the intestinal tract due to difference in bacterial flora and growth. One only needs to recall the years spent before trichomonads were successfully and regularly cultured from the vagina. This study is particularly important. Negative findings are just as important as positive ones. Even so, confirmation is desirable to establish proof beyond reasonable doubt.

DR. ALLEN (Closing).—We were quite disappointed with our findings, particularly in the rectum, because we felt that in previously reported patients the workers had either used lubricants or jellies to get out the rectal material or other methods which we thought might give indefinite results. We felt also that we might find them in the pelvic organs. We still feel that patients should not be operated upon in the presence of the streptococcus which accompanies *Trichomonas*.

Oftentimes we have referred the husbands of these women to an urologist, many times with a negative result. On repeated examinations, however, trichomonads of the prostate have been recognized.

Chronic prostatitis is so common it may well be a cause of vaginitis, with the trichomonads as secondary invaders.

We still have to find out how the *Trichomonas* gets into the vagina.

VINBARBITAL SODIUM* FOR OBSTETRIC AMNESIA, ANALGESIA, AND ANESTHESIA

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SINCE 1929, we^{1, 2} have used the various barbituric acid derivatives both orally and intravenously in an effort to find a simple, safe, and satisfactory method for the relief of pain during parturition that would not require any particular skill for its administration.

Recent favorable reports by Bernstine and Prince³ and Evans⁴ on the oral and intravenous administration of vinbarbital sodium for the production of amnesia and analgesia led us to investigate further vinbarbital sodium, alone or in combination with scopolamine, for the induction of amnesia, analgesia, and anesthesia during labor.

The material presented in this report represents 622 unselected patients that were attended by the author on the obstetric service of this hospital. The patients were divided into two main groups for tabulation and analysis.

Group One.—Included in this group were 469 patients, 299 of whom were primiparas and 170 multiparas. All patients received vinbarbital sodium orally in combination with scopolamine and in addition vinbarbital sodium intravenously for the completion of labor.

Group Two.—Included in this group were 153 patients. Sixty were primiparas and 93 were multiparas, to whom vinbarbital sodium intravenously was the only analgesia and anesthesia administered.

Group One

Method of Administration.—In our previous experience with the other barbiturates for the alleviation of pain during labor, three to six grains in combination with scopolamine was insufficient in the majority of instances to produce satisfactory amnesia and analgesia. Vinbarbital sodium then was administered in increasing amounts until the desired effect was obtained. After careful study, it was determined that the average oral dose was nine grains.

The initial dose of nine grains of vinbarbital sodium with $\frac{1}{150}$ grain of scopolamine was given when the patient was in active labor with uterine contractions recurring every four to five minutes, or at any time the patient was complaining. Thereafter, $\frac{1}{200}$ grain of scopolamine was given each hour as needed to maintain amnesia and analgesia. The number of scopolamine injections varied from one to three, and the average patient received two injections. Vinbarbital sodium, ten to twenty grains, administered intravenously, was the anesthesia used at the time of delivery.

If, at any time during the course of labor, however, the patient became unduly restless, the intravenous administration of five to ten grains of vinbarbital sodium was given immediately, and repeated as necessary.

Earlier in this study, restlessness was controlled at the time of delivery with local anesthesia. This was used in fifty-five patients. Later it was found that additional vin-

*Vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate, and is distributed under the name of "Delvinal" sodium. The material used in this study was provided through the courtesy of the Medical-Research Division, Sharp & Dohme, Inc., Philadelphia, Pa.

barbital sodium was more effective and, furthermore, it had the added advantage that it could be given at any time the patient became restless.

Dosage.—The average dose of vinbarbital sodium was nine grains orally and ten grains intravenously. The largest combined dose was 38 grains, 18 grains orally and 20 grains intravenously, in a 46-hour labor, without any deleterious effect upon the mother or infant. One hundred and five patients, or 22.1 per cent, received five grains intravenously. Two hundred and sixty-six patients, or 56.7 per cent, received ten grains; 76 patients, or 16.2 per cent, received fifteen grains; and 22 patients, or 5 per cent, received 20 grains.

As may be seen, there was a wide variation in dosage of the vinbarbital sodium administered intravenously. This depended entirely on the response of the patient, and we endeavored to individualize the dose to the patient. Therefore, some received only five grains, while others required as much as 20 grains, intravenously. The majority (56.7 per cent) required 10 grains both for the successful control of restlessness and the completion of labor. In no case did these doses cause any depression or retardation of labor.

Time Interval.—Two hundred and seventy patients, or 57.5 per cent, of Group One received vinbarbital sodium orally with scopolamine from two to four hours before delivery; one hundred and thirty-five patients, or 26.6 per cent, within four to eight hours of delivery; forty-one patients, or 9.5 per cent, within 8 to 12 hours of delivery; and twenty-two patients, or 6.4 per cent, from 12 to 18 hours before delivery.

Two hundred and eighty-seven patients, or 61.1 per cent, had complete amnesia from vinbarbital sodium orally with scopolamine.

Two hundred and fifteen patients, or 45.8 per cent, of Group One received vinbarbital sodium intravenously from 10 to 40 minutes; ninety-nine patients, or 21.1 per cent, from 40 to 60 minutes; 92 patients, or 19.5 per cent, from 1 to 1½ hours; 30 patients, or 6.3 per cent, from 1½ to 2 hours; 15 patients, or 3.1 per cent, from 2 to 3 hours; and 18 patients, or 2.8 per cent, from 3 to 4 hours prior to delivery.

Amnesia was complete in all instances after the intravenous administration of vinbarbital sodium.

TABLE I. ANALYSIS OF 469 CASES ACCORDING TO PARITY AND TYPE OF DELIVERY

Spontaneous Delivery	186—39.4%	Operative Delivery	284—60.5%
Primiparas	72	Primiparas	227
Multiparas	113	Multiparas	57
Low forceps		262—92.2%	
Breech extraction		19— 6.6%	
Midforceps		3— 1.2%	

Among the 469 patients in this group, spontaneous delivery occurred in 186, or 39.4 per cent. Operative delivery occurred in 284, or 60.5 per cent. Although the operative deliveries were increased in this series, 62 per cent were primiparas and 92.2 per cent were elective or outlet forceps. Of the remaining operative cases, there were nineteen breech extractions and three midforceps deliveries.

The stillbirth and neonatal mortality rates for the 470 infants in Group One (one set of twins) are shown in Table II. There were nine cases in which the infant was lost, giving a total stillbirth and neonatal mortality rate of 1.9 per cent. Among the nine babies that were lost, three (one anencephalic monster, one prolapsed cord, and one macerated infant in a diabetic mother) died before the onset of labor. All, of course, were in no way affected by the drugs used.

Among the six remaining neonatal deaths, there were three nonviable infants, including twins, and the drugs were in no way responsible for their deaths.

There were two full-term babies who died from congenital atelectasis 36 and 42 hours after spontaneous delivery. Both of these infants were subjected to autopsy. One was slightly asphyxiated at birth and one was not. One seven and one-half months premature

infant, weighing four pounds and four ounces, delivered spontaneously, but was moderately asphyxiated at birth and died 43 hours later. The question naturally arises whether the analgesics may not have contributed to the pulmonary atelectasis. It is our opinion that they may have been a contributing factor in the 7½ months premature infant.

If we are allowed to deduct the three infants that died before the onset of labor and the three nonviable infants, our corrected mortality was three, or 0.43 per cent.

TABLE II. FETAL MORTALITY

Stillbirth (died before the onset of labor)	3
1 monstrosity	
1 prolapsed cord	
1 macerated fetus, diabetic mother	
Neonatal deaths	6
Full term	2
Congenital atelectasis (autopsy)	
(One was asphyxiated, 1 was not)	
Premature	4
3 nonviable infants (1 set twins)	
1 7½ months infant, lived 43 hrs.	
(moderately asphyxiated)	
Total infants lost	9
Gross mortality	1.90%
Corrected mortality	3 or 0.43%
(Congenital atelectasis, 2 full term and 1 7½ months premature infant)	

Group Two

Vinbarbital sodium intravenously was the only analgesia and anesthesia used in this group. The amount necessary for a spontaneous or an operative delivery with repair was somewhat smaller than in the first group.

One hundred and fifty-three patients in this group in whom delivery occurred in one to two hours after admission to the hospital received an initial dose of ten grains of vinbarbital sodium intravenously as soon as possible after admission. If the initial dose was not sufficient to produce satisfactory analgesia and anesthesia, an additional five to ten grains were administered. The average dose was 15 grains and the maximal dose did not exceed 25 grains.

Seven patients received only five grains of vinbarbital sodium intravenously, but three of these had local anesthesia. Fifty-nine patients, or 38.4 per cent, received ten grains; 63 patients, or 41.1 per cent, received 15 grains; and four patients, or 2.6 per cent, received 25 grains.

Ninety-one patients, or 59.3 per cent, received vinbarbital sodium intravenously within thirty minutes before delivery; thirty-three patients, or 22 per cent, within thirty minutes to one hour before delivery; and twenty-eight patients, or 18.7 per cent, from one to two hours before delivery.

It is likely that intravenous vinbarbital sodium will find its greatest field of usefulness in this group. The "screaming" parturient who is nearing the end of her labor can be rapidly and effectively calmed with an injection of the drug.

There were sixteen patients, or 10 per cent, in this group in whom restlessness at the time of delivery was effectively controlled by local anesthesia.

Included in this group were two patients with primary uterine inertia that could not be given sufficient vinbarbital sodium to produce complete amnesia without retarding labor. They were given five grains of vinbarbital sodium intravenously and delivery was completed under local anesthesia.

Complete amnesia was obtained in 151 cases, or 99 per cent, in this group.

Among the 153 patients in this group, spontaneous delivery occurred in 80, or 50.9 per cent; operative delivery occurred in 77, or 49 per cent. Thus, it is seen that the incidence of

spontaneous and operative deliveries was practically the same in this series. In the operative deliveries, 80.5 per cent were elective or outlet forceps. Of the remaining operative cases, there were eleven breech extractions and four midforceps deliveries, showing rather conclusively that vinbarbital sodium in no way retards labor and is equally effective in both spontaneous and operative delivery.

TABLE III. ANALYSIS OF 153 CASES ACCORDING TO PARITY AND TYPE OF DELIVERY

Spontaneous delivery	80—50.9%	Operative delivery	77—49.0%
Primiparas	20	Primiparas	40
Multiparas	56	Multiparas	37
Low forceps		62—80.5%	
Breech extraction		11—14.2%	
Midforceps		4— 5.1%	
(4 twin deliveries—157 infants)			

TABLE IV. FETAL MORTALITY

Stillbirths (died before the onset of labor)	6
1 monstrosity	
2 pre-eclampsia (7½ and 8 months)	
1 macerated infant, cause unknown	
1 cord around the neck	
1 fetal heart not heard on admission, no fetal movements felt 4 days prior to labor	
Neonatal deaths (all premature)	4
3 nonviable infants (1 set of twins)	
1 7½ months infant, lived 24 hours, was not asphyxiated	
Total infants lost	10
Gross mortality	6.3%
Corrected mortality (1 7½ months premature)	0.6%

The stillbirth and neonatal mortality rates for 157 infants in this group (4 sets of twins) are shown in Table IV. There were ten instances in which the infant was lost, giving a total stillbirth and neonatal mortality of 6.3 per cent. Among the ten babies lost, however, six died before the onset of labor. There were one 6½ months monstrosity, one 7½ months premature infant in a patient with pre-eclampsia, one 8 months premature infant in a patient with pre-eclampsia, and one full-term infant in whom the cord was found wrapped tightly around the neck at birth. Included also were one full-term infant in which the mother had not felt life for four days prior to labor and on admission to the hospital no fetal heart was heard, and one full-term macerated infant for which the cause of death was unknown. Vinbarbital sodium, of course, played no part in these six deaths, since no fetal heart was heard on admission to the hospital.

In the four neonatal deaths, all premature, three were nonviable. One was a six months' premature infant, not asphyxiated at birth and who lived 24 hours, and there were 7 months' premature twins, with marked asphyxia at birth and who lived 6 hours. The remaining neonatal death was in a 7½ months' premature infant, not asphyxiated at birth and who lived 24 hours. If we are allowed to deduct the three nonviable infants and the six infants that died before the onset of labor, our corrected fetal mortality was one, or 0.6 per cent.

Effect on Infants

Classification of asphyxia.—

1. Infants in whom the initial respiration was delayed for thirty seconds or more and required only the clearing of the air passages were classified as mildly asphyxiated.

2. Infants in whom the initial respiration was delayed more than sixty seconds and required, in addition to clearing the air passages, carbon dioxide and oxygen for resuscitation were classified as moderately asphyxiated.

The color of all infants in both groups was good. No great difficulty was encountered in the establishment of respirations in any infant that was asphyxiated. No respiratory stimulant other than carbon dioxide and oxygen was required.

TABLE V. EFFECT OF THE DRUGS ON 618 LIVING INFANTS

	TOTAL INFANTS BORN ALIVE	CRIED SPONTANEOUSLY		MILD ASPHYXIA		MODERATE ASPHYXIA	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Group One	467	405	86.7	53	11.1	9	2.1
Group Two	151	125	82.7	19	12.5	6	3.9
Total	618	530	85.7	72	11.6	15	2.4

Group One.—There were 467 living babies delivered in this group. Four hundred and five, or 86.7 per cent, breathed and cried spontaneously. Fifty-three babies, or 11.1 per cent, were classified as mildly asphyxiated but required no resuscitation. Nine infants, or 2.1 per cent, were classified as moderately asphyxiated and required carbon dioxide and oxygen for resuscitation.

Group Two.—There were 151 living babies delivered in this group. One hundred and twenty-five, or 82.7 per cent, breathed and cried spontaneously. Nineteen babies, or 12.5 per cent, were classified as mildly asphyxiated but required no resuscitation. Six babies, or 3.9 per cent, were classified as moderately asphyxiated. Included in this group were three nonviable infants.

The majority of infants breathed and cried spontaneously regardless of the time elapsing between the administration of the drug and the delivery of the infant.

The size of the dose of vinbarbital sodium evidently played only a minor role in the incidence of asphyxia in this series.

TABLE VI. COMBINED STILLBIRTH AND NEONATAL MORTALITY IN GROUPS ONE AND TWO

Stillbirths	9
(all died before the onset of labor)	
Neonatal deaths	10
Full term	2
(Congenital atelectasis)	
Premature	8
6 nonviable infants	
2 7½ months infants	
Total infants lost	19
Gross mortality	3.30%
Corrected mortality—4 infants or	0.63%
(2 full term, congenital atelectasis)	
(2 7½ months premature infants)	

The combined stillbirth and neonatal mortality rates for the 627 infants (five sets of twins) are shown in Table VI. There were 19 infants lost in the entire series, giving a total stillbirth and neonatal mortality rate (uncorrected) of 3.3 per cent. However, of the 19 infants that were lost, nine died before the onset of labor. In the ten neonatal deaths, there were six nonviable infants.

If we are allowed to deduct the nine infants that died before the onset of labor and the six nonviable infants, our corrected fetal mortality was four, or 0.63 per cent.

Effect on the Mother

The intravenous administration of vinbarbital sodium was usually given by the author or the resident house staff and occasionally by the delivery room nurse. The intravenous preparation is a solution of one grain of vinebarbital sodium per cubic centimeter in propylene glycol and distilled water. A ten cubic centimeter syringe with a twenty gauge needle was used for the injection. The solution was injected into any available vein

in the arm or hand. The rate of injection was governed by the individual response. The usual time required for the injection of ten cubic centimeters was from one to two minutes, although caution should always be practiced. There was seldom any indication to alter the rate of the injection. Vinbarbital sodium was given intravenously by at least fifteen different physicians and nurses, many of whom had only meager knowledge of the preparation, yet no serious effects or incidents were reported attributable to overdosage of the drug.

After the intravenous administration of vinbarbital sodium, the rapidity and ease with which the patient fell asleep was impressive. Deep sleep came within from one to two minutes. There was no noticeable change in cardiac or respiratory rates. There was no change in blood pressure, except in those patients who exhibited an elevated blood pressure on admission. In these, there was usually a decline of from ten to twenty millimeters of mercury, but this was transitory and the blood pressure returned to the original level within from ten to twenty minutes.

Duration of Labor

There was no apparent effect on the duration of labor. After the intravenous administration of vinbarbital sodium, the uterine contractions were accelerated and dilatation progressed rapidly in the majority of cases. The expulsive powers at the time of delivery were only slightly diminished.

The length of labor in this series of 622 cases was carefully recorded. In Group One sixteen patients, or 3.4 per cent, had labors of less than two hours' duration; 148, or 31.8 per cent, from two to six hours; 166, or 35.3 per cent, from six to twelve hours; 82, or 17.4 per cent, from 12 to 18 hours; 39, or 8.3 per cent, from 18 to 24 hours; and 18, or 3.8 per cent, from 24 to 48 hours.

In Group Two twenty-one patients, or 13.7 per cent, had labors of less than two hours duration; 70 patients, or 45.7 per cent, from two to six hours; 37, or 24.1 per cent, from six to twelve hours; 11, or 7.1 per cent, from 12 to 18 hours; and 14, or 9.1 per cent, from 18 to 36 hours.

The shortest labor was 55 minutes and the longest was 48 hours. Only 24 patients, or 3.8 per cent, of the entire series had labors of more than 24 hours' duration.

Five hundred and fifty-one cases, or 88.5 per cent, both spontaneous and operative deliveries, received no additional anesthesia. Local anesthesia was used in 71 cases, or 11.5 per cent, for the control of restlessness at the time of delivery.

Restlessness

All barbiturates, alone or in combination with scopolamine, are prone to cause restlessness during uterine contractions.

In this series, 110 patients, or 17.7 per cent, were restless. Sixty-three were classified as mild and 47 as moderate, all of whom were readily and effectively controlled with additional vinbarbital sodium, five to ten grains intravenously.

Prior to this investigation, restlessness was the chief disadvantage of barbiturates in obstetric analgesia. Having the patient restrained until she was given some type of inhalation or local anesthesia for delivery was an annoying complication. With the present technique, "restlessness is conspicuous by its absence." This is particularly gratifying to those in attendance at delivery.

Recovery Period

Duration of vinbarbital sodium anesthesia is variable depending on a number of factors, i.e., the constitution of the patient, the length of labor, and the total dosage used. The majority of the patients slept soundly and quietly for from one to eight hours following delivery. At the end of this time, varying degrees of restlessness did occur in approximately 10 per cent of the patients, but these were easily controlled with small doses of morphine sulphate. None required any form of restraint. Restlessness in the recovery period may constitute one of the disadvantages of vinbarbital sodium, although in the majority of instances the recovery phase was smooth and quiet. Two patients were found

out of bed. Ten patients tried to get out of bed. The time of occurrence of these accidents varied from one to eight hours after delivery. There was no relation to dosage. The patients themselves had no recollection of their behavior. Postoperative vigilance by the nursing staff is imperative, however, until denarcotization is complete.

A few patients complained of blurred vision or faulty accommodation for several hours after they were awake, but all stated that this was not unpleasant. There was no nausea or vomiting. All patients were very enthusiastic about the results obtained and, when questioned, each expressed a desire for the same method of analgesia and anesthesia for their future deliveries.

Contraindications

During this study, no patients were encountered in whom this method for induction of analgesia and anesthesia was contraindicated.

There are, of course, some instances in which the use of vinbarbital sodium and scopolamine may be unwise for obvious reasons. We prefer caudal anesthesia in the presence of acute upper respiratory infections, cardiac lesions, with or without decompensation, diabetes mellitus, tuberculosis, and premature labors.

Complications

In this series, two patients were considered pre-eclamptic, and there was one patient who developed antepartum eclampsia. Seven patients had primary uterine inertia. Postpartum hemorrhage occurred in five cases, or 0.8 per cent. There were two cases of premature separation of the placenta and one case of placenta previa. Two patients developed postpartum psychosis. These patients were all given vinbarbital sodium with good results. All delivered living normal babies except the two pre-eclamptic patients, and their babies died before the onset of labor.

The intravenous administration of any agent always presents the danger of extravasation. This occurred in one patient to whom vinbarbital sodium was being administered for the control of restlessness. Ten cubic centimeters accidentally were injected subcutaneously and resulted in a first degree "burn" around the antecubital area and a partial ulnar nerve paralysis. This was the only complication resulting from the drug in the entire series.

Summary and Conclusions

1. Six hundred and twenty-two patients received vinbarbital sodium for induction of amnesia, analgesia, and anesthesia during labor.

2. Four hundred and sixty-nine received vinbarbital sodium orally in combination with scopolamine and, in addition, vinbarbital sodium intravenously for the completion of labor. The average dose was nine grains orally and ten grains intravenously.

3. There were 153 patients who received no other medication than vinbarbital sodium intravenously for induction of analgesia and anesthesia. The average dose was 15 grains.

4. Four hundred and fifty-nine, or 57.7 per cent, were primiparas, and 263, or 42.2 per cent, were multiparas.

5. Spontaneous delivery occurred in 266, or 42.5 per cent. Operative delivery occurred in 361, or 57.5 per cent. Of the operative deliveries, 324, or 89.7 per cent, were elective or outlet forceps, 30, or 8.3 per cent, were breech extractions and 7, or 1.9 per cent, were midforceps deliveries.

6. Of the 618 infants born alive, 530, or 85.7 per cent, breathed and cried spontaneously. Seventy-two, or 11.6 per cent, were slightly asphyxiated but required no resuscitation. Fifteen infants, or 2.4 per cent, were moderately asphyxiated and required only carbon dioxide and oxygen for resuscitation.

The time elapsing between the administration of the drug and delivery or the size of the dose of vinbarbital sodium played insignificant roles in the incidence of asphyxia in this series.

7. The uncorrected fetal mortality was 3.3 per cent. Of the 19 infants that were lost, nine died before the onset of labor and there were six nonviable infants. The corrected fetal mortality was four, or 0.63 per cent.

8. Vinbarbital sodium appeared to have no effect on the duration of labor. Two hundred and fifty-five patients, or 40.9 per cent, were in labor less than 6 hours; 203 patients, or 32.6 per cent, from 6 to 12 hours; 140 patients, or 22.5 per cent, from 12 to 24 hours; and 24 patients, or 3.8 per cent, from 24 to 48 hours. After the intravenous administration of vinbarbital sodium, the uterine contractions were accelerated and dilatation progressed rapidly in the majority of cases. It was equally effective in both spontaneous and operative deliveries.

9. The "screaming" parturient who is nearing the end of her labor can be rapidly and effectively calmed with intravenous vinbarbital sodium.

10. Slight to moderate degrees of restlessness occurred in 181 patients, or 29 per cent. Seventy-one patients who were slightly restless at the time of delivery were effectively controlled with local anesthesia. One hundred and ten patients who were restless during labor were promptly controlled by additional administration of intravenous vinbarbital sodium.

11. Complete amnesia was obtained in 61.6 per cent of all patients who received vinbarbital sodium orally with scopolamine. Complete amnesia was obtained in 620, or 99 per cent, following the intravenous administration of vinbarbital sodium.

12. No patients were encountered in whom this method of analgesia and anesthesia was contraindicated.

13. No inhalation anesthesia was required in any instance.

14. The incidence of postpartum hemorrhage was not increased. It occurred in five patients, an incidence of 0.8 per cent.

15. The majority of patients slept soundly for from one to eight hours following delivery. All expressed a desire for the same method of analgesia and anesthesia for their future deliveries.

16. There was no maternal mortality in the entire series. There was only one complication. This resulted from the accidental injection of vinbarbital sodium into the subcutaneous tissue.

17. The results obtained in 622 unselected private patients indicate that vinbarbital sodium is a most satisfactory agent for the induction of obstetric amnesia, analgesia, and anesthesia.

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PREGNANEDIOL EXCRETION AT THE ONSET OF LABOR

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IN THE search to identify factors concerned with the initiation of labor, attention has been directed toward the status of hormones during pregnancy and labor. It has been established that hormonal factors are responsible for the maintenance of pregnancy.¹³ Of the hormones, the steroids undoubtedly play a significant role. In pregnancy, some of the urinary steroids appear to increase in the amount excreted in gradual wave-like steps, with the greatest acceleration during the last trimester of pregnancy. Of those steroids which so increase, the quantities recoverable appear to be roughly proportional to the growth of the fetus and placenta.

During pregnancy, the salient steroid hormone is progesterone, which is essential to the establishment and maintenance of gestation. It has been reduced to pregnanediol through a series of physiologically inactive intermediaries, by Butenandt and Schmidt,⁵ and by Westphal and Buxton.¹⁸ Conversely, pregnanediol has also been oxidized to progesterone by Butenandt and Schmidt.⁵

From these transformations, pregnanediol, the inactive alcohol isolated by Marrian in 1929 from the urine of pregnant women, appears to be the end-product of a series of intermediate steps in the metabolism of progesterone. These metabolites consist of the physiologically inactive substances, pregnanediol, a hydroxyketone, and finally pregnanediol, which is the major end-product of progesterone metabolism. The inactive intermediaries appear to make up a relatively small proportion of the recoverable steroids. Pregnanediol is conjugated in the body with glucuronic acid and is then excreted by the kidney, appearing in the urine as sodium pregnanediol glucuronide (NaPG). The purpose of this study is to measure the excretion of this substance in the urine in the days immediately preceding the onset of labor, during labor, and during the first few days of the puerperium.

Consideration of the site of origin brings out that pregnanediol may have sources other than progesterone. No other source has ever been shown to produce a significant amount of the substance, nor of its precursor, progesterone. Accordingly, it is reasonable to assume that the major fraction of the substance recovered in the urine of pregnant women is of placental, and in turn, of progesterone origin. However, in the glucuronic acid titration method which was used in the determinations here reported, several components of the androstane series and some inactive steroids of the pregnane series will be carried through the extraction process and be precipitated by lead nitrate, so that their glucuronic acid fraction will comprise a portion of the total assay. Since this fraction is relatively small and constant, it does not appear to detract from the essential significance of the findings presented.

Progesterone is furnished initially by the corpus luteum and subsequently by the placenta, at least as to its largest fraction. Fundamentally, the placenta must survive in order to maintain the physiologic status of pregnancy. This was shown by Van Wagenen and Newton,¹⁵ who removed the fetuses from maeaque monkeys in the last third of pregnancy, leaving the placentas in place. These pregnancies progressed to term, during which the animals gained weight after they recovered from the transitory weight loss at the time of operation. Removal of the fetus has been repeated in rats and guinea pigs with similar results. Also, there are a few instances of placental retention in the human.^{17*} All of these observations show that, although the fetus be removed, pregnancy can continue, provided the placenta remains in place and functions. This consideration suggests that the placenta is the anatomic site for regulation of the duration of pregnancy. The mechanism by which this is accomplished seems to be by the production of hormones by an intact placenta.

Consideration of the hormonal factors preceding parturition recalls Rosenkrantz¹² observation on thirty cases of prolonged labor, wherein the estrin and progestin contents of the placentas were assayed. Approximately half of the normal amount of estrin was found in the presence of a normal amount of progestin. From this, progestin appears to exert an inhibitory effect on the myometrium.

The contention that labor occurs because of progesterone deficiency is supportable from observations on animals in which the ovaries are essential for the continuation of pregnancy. Abortion invariably occurs following the removal of the corpora in the rabbit.³ It also occurs in the rat. In women with hemochorial placentas, the ovaries are not so essential after the first trimester, and the effect of removal of the corpora on this phase is less marked. However, premature labor often follows rather slight alterations (i.e., bleeding) in the placenta.

Moreover, pregnancy has been prolonged by giving progesterone to rabbits just before term.⁸ This has also been done by reviving a waning corpus luteum, as late as the 28th day in rabbits, by administering estrin.⁹ Snyder¹³ accomplished deferral of parturition by inducing new functional corpora (when the originals had waned) by employing chorionic gonadotrophin, this method serving as another means of furnishing progesterone.

From these considerations it seems logical to conclude that the withdrawal of progestin is a prerequisite to the onset of labor. The chief basis for this contention was the drop in the pregnanediol of the urine, which has been demonstrated during many cases of threatened or recurrent abortion.

From the pregnanediol excretion curve of Venning and Browne¹⁶ there is no very abrupt drop prior to the onset of labor. Our own observations are not wholly in agreement with these earlier investigators. Due to the physio-

*Willard M. Allen, of St. Louis, has kindly permitted the author to refer to a case of abdominal pregnancy in which the excretion of NaPG was determined after the delivery by abdominal section of a full-term, living fetus. In this case the placenta was not removed at the time of delivery. The excretion of NaPG was maintained at a high level for about three weeks after delivery of the fetus, thereby showing that the fetus is not the source of the precursors of pregnanediol.

logic lag from administration of progesterone to excretion as sodium pregnanediol glucuronide, the failure of a dramatic drop in NaPG values prior to the onset of contractions is not necessarily associated with a high or relatively high level of progesterone. The reasoning is as follows: When 200 mg. of an orally active progestin is given daily, the amount of pregnanediol excreted in the urine is approximately 55 mg. The increase in output is observed from 36 to 48 hours after the oral administration. Moreover, Allen and his co-workers² report that progesterone withdrawal bleeding appeared while the pregnanediol level was still almost as high as it had been at the peak of the medications. This suggests that there is a definite lag of about two days before clearance of the pregnanediol is observed, even though the effect of a considerably lower level has become clinically apparent. Hence, this should be considered in interpreting the pregnanediol excretion graphs. The uterus would probably not be kept from contracting effectually by the amount of progesterone which, for example, was converted to only 4 mg. of NaPG in a day.

Plan and Method

Sodium pregnanediol glucuronide assays were made on women in late pregnancy. The titrimetric method of Allen and Viergiver,¹ with a modification of extraction technique suggested by Woolf, Viergiver, and Allen,²⁰ was followed in the determinations. This procedure differs from previous methods by the precipitation of the pregnanediol glucuronide from aqueous solution as a lead salt. Pregnanediol is then measured by titrating the amount of glucuronic acid liberated by acid hydrolysis. The glucuronic acid is titrated with Shaffer-Hartmann-Somogyi copper reagent.

Twenty-four-hour volumes of urine were obtained from the patient at home, or in cases of patients in the hospital, from routine ward voidings. Generally, the patient alone made the most complete collections. The 24-hour specimens were extracted with 300 ml. of butyl alcohol during collections.

Checks on the method of assay, using aliquots of 24-hour urines, were consistent and revealed almost identical values. Administration of a progestin is reflected clearly by this method. Twenty-four-hour values assayed by the glucuronic acid method, except for being slightly lower, compare quite well otherwise with established figures for pregnanediol outputs in the first 38 weeks of normal pregnancy as determined by other methods. Sixty-eight pregnant women have had sodium pregnanediol glucuronide assays during the latter phase of their pregnancy, during parturition, and for a few days post partum. Composite graphs indicate that there is ordinarily a pronounced fall in the NaPG excreted in the urine during the last several days preceding the onset of spontaneous labor. For purposes of this investigation, cases of spontaneous delivery have been divided into three major groups: spontaneous onset of premature labor; spontaneous labor at term; and spontaneous postmature labor.

Results

Earlier studies have indicated quite high levels of pregnanediol at the onset of labor, as described by Venning (1935),¹⁶ Stover,¹⁴ Wilson,¹⁹ and Bachman and Hirschmann.⁴ However, Bachman and Hirschmann⁴ observes not only cyclic monthly fluctuations in the amount of pregnanediol excreted, but a pronounced fluctuation immediately preceding the onset of labor. Apparently, the levels he reported for the beginning of labor were the lowest found by any observer who used the original Venning and Browne technique. Although he studied only a few cases, from his charts, labor appeared to begin in the excretion range of 30 to 40 milligrams daily. In our hands, using the more recent glucuronic acid method, the NaPG excretion values have been appreciably lower, so that we are unable to confirm reports of the higher levels found at the onset of labor by prior investigators.

Since pregnanediol presumably comes from progesterone secreted by the placenta, it might be of interest to record the findings in the event of sudden termination of pregnancy. Such an opportunity was presented by twelve patients who had cesarean sections (Fig. 1) and on whom 24-hour urinary collections were made during the day or so they were in the hospital prior to operation. These situations represent a somewhat premature interruption of pregnancy, in which the patient would ordinarily not have fallen in labor for at least a few days after the date chosen for the operation. The sections were carried out at an average of five days prior to term, and, although the NaPG values at 24 hours preceding the operation, and on the day of operation, were at relatively low levels for this duration of pregnancy, i.e., 21 and 18 mg. respectively, the sudden decrease in level following the removal of the placenta is notable. For example, an average of 7.5 mg. of NaPG was found on the first postoperative day. The average at the second postoperative day was 3.6 mg., and thereafter approximated the postpartum averages.

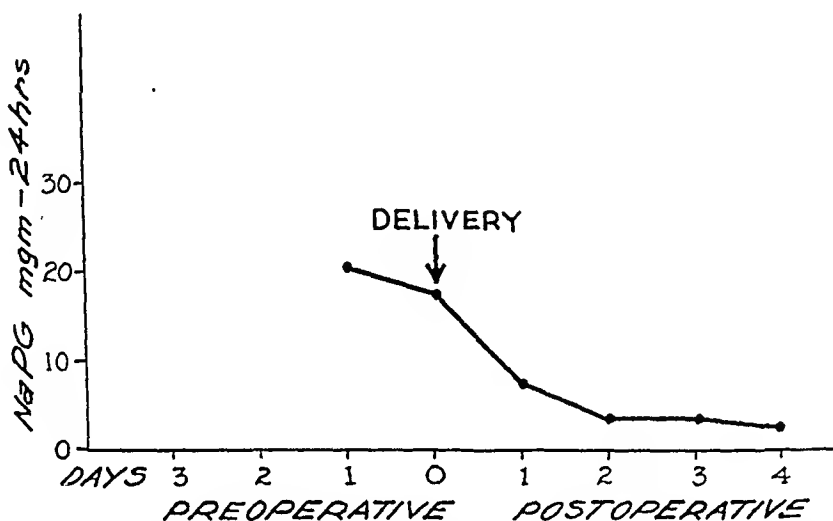


Fig. 1.—Pregnanediol concentration following cesarean section. Averages of twelve cesarean sections carried out in the last few days of pregnancy, showing moderately high NaPG values, such as are found a very few days prior to the spontaneous onset of labor. There is an immediate sharp postoperative decline.

During the last few days of pregnancy, the values of pregnanediol recovered progressively declined from the high values ordinarily found at the peak (38th week) of normal pregnancy. The fall is considerably more rapid than the corresponding increase which occurred during the slow growth of the first 37 or so weeks of pregnancy, where the daily peak amounts excreted may reach levels of 80 mg., as measured by the glucuronic acid titration method. Even in toxemias of pregnancy, or where the fetus had died during late pregnancy, the daily output of NaPG is usually greater than 40 mg. at some time in the last trimester of the pregnancy. Thus, the lower NaPG values found as the onset of labor approaches uniformly represent a relatively rapid fall from considerably higher concentrations. This decline in pregnanediol, which begins some two weeks prior to the onset of labor, gradually accelerates so that it is considerably more abrupt during the last six days than at any earlier time during the falling off period.

The composite of 68 spontaneous delivery assays (Fig. 2) shows a steady decline from an output of approximately 30 mg. of sodium pregnanediol glucuronide four days before delivery took place. One day prior to the onset of labor, the average output of NaPG had been 14.8 mg., while 48 hours preceding labor, the average was 19.5. The day of delivery shows an average excretion of 12.5 mg. The next day (post partum 1) the values dropped to 8.8 mg., then on the second day to 4.6 milligrams.

Thus it may be seen that the fall is progressive, a drop of 25 per cent over the previous day's level being observed during the first 24 hours post partum. From here on the

drop is less precipitous, but continues rather regularly until levels of about 4 mg. are found daily. This is about the quantity found in association with an active corpus luteum of menstruation. We were unable to confirm Heckel's⁷ findings of zero NaPG output on some days of the early postpartum period.

The average outputs of the 14 cases in which delivery occurred at term revealed a significant decline in pregnanediol excretion (over 50 per cent), in the 72 hours preceding termination of the third stage of labor. Since there appears to be a lag of nearly 48 hours in the metabolism and excretion of pregnanediol,² it is probable that the true conditions prevailing at the time of labor are more nearly represented by the amount of pregnanediol present at the second postpartum day. This concept seems to be supported by the data from both spontaneous delivery and cesarean section.

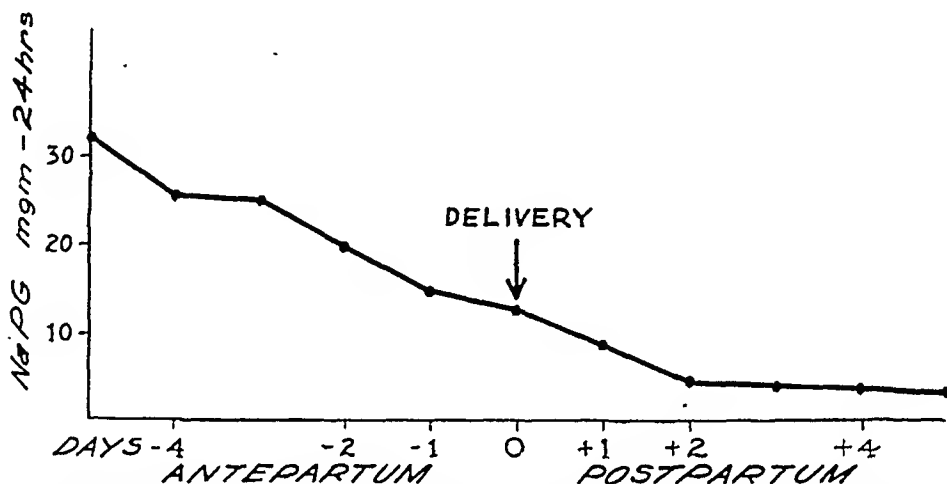


Fig. 2.—Pregnanediol concentration at the onset of labor (delivery spontaneous). Composite graph of 68 cases showing daily excretion of NaPG in milligrams, including spontaneous term, premature, and postmature deliveries.

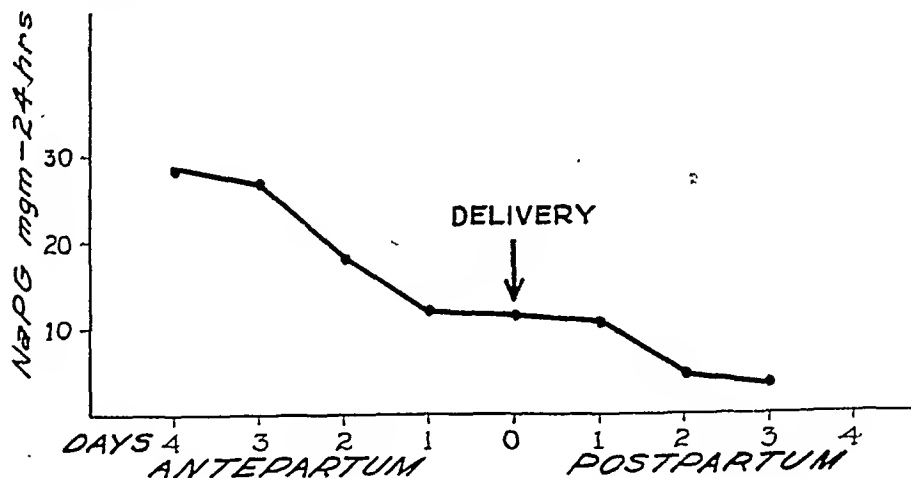


Fig. 3.—Pregnanediol concentration at the onset of labor. Term spontaneous delivery composite graph (14 cases) which show a typical steady diminishing NaPG output. The first postpartum day value of term delivery is somewhat higher than the average of all spontaneous deliveries.

Those deliveries which occurred a week or more after term, with fetuses above average weight, composed a segment of 22 cases. Their averages are shown in the postmature delivery composite graph of Fig. 4. Delivery occurred at a slightly lower average level of NaPG than in the term deliveries. Moreover, the decline in urinary pregnanediol concentration extending over the week prior to delivery was considerably more gradual than that of either term deliveries or premature deliveries. The postpartum course essentially followed that of the other groups.

The premature deliveries composed a series of 34 instances, which, at the onset of labor, had an average output of 13.5 mg. of NaPG. The week preceding the onset of labor revealed a more marked decline than that for the term or postmature series. Since this group was composed mainly of spontaneous premature rupture of the membranes, it might be expected that in these situations the decline would be quite rapid. The postpartum level was essentially the same in the premature delivery group as in each of the other series.

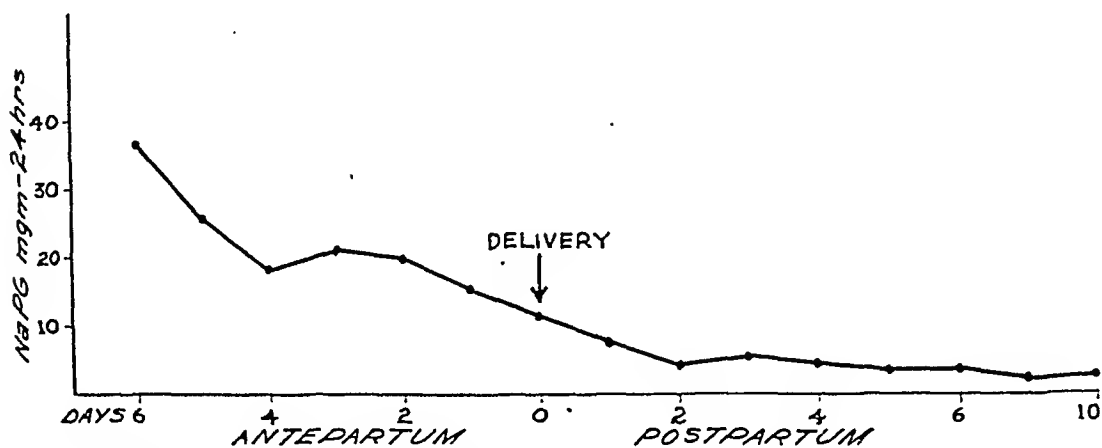


Fig. 4.—Pregnanediol concentrations at the onset of labor. Spontaneous delivery of 22 cases showing the postpartum values ordinarily found over an extended period.

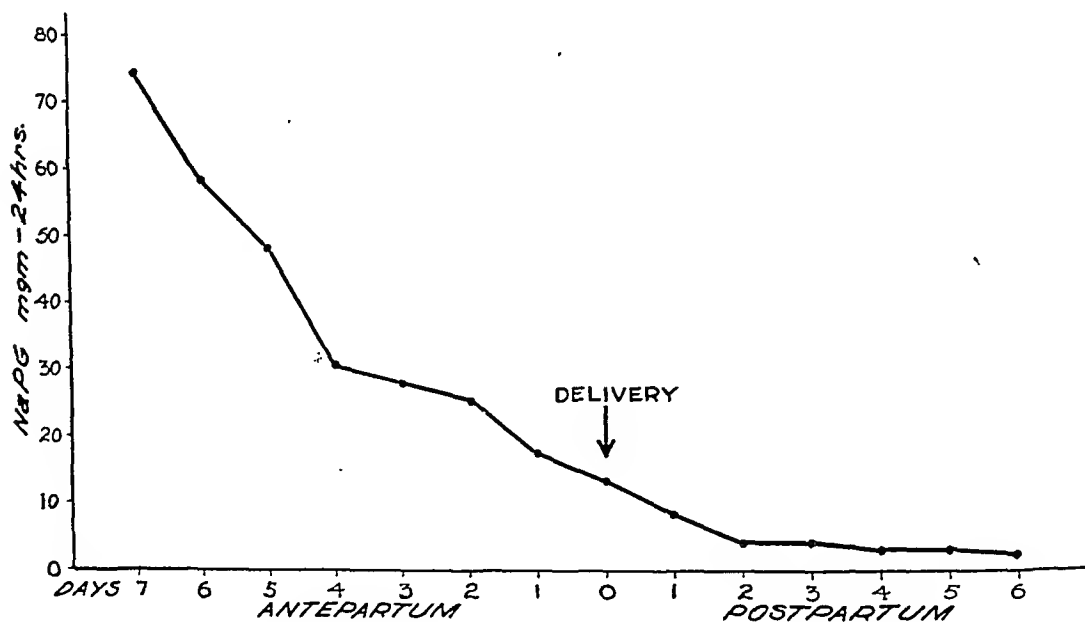


Fig. 5.—Pregnanediol concentration at the onset of labor. Spontaneous premature delivery of 34 cases shows a relatively steep antepartum fall in NaPG. The postpartum values agree with those found in term delivery and in the composite (Fig. 2) of all deliveries.

Whether labor begins prematurely (Fig. 3) or postmaturely (Fig. 4), the pregnandiol levels at that time are found within a relatively narrow range; that is, from 12 to 15 mg. daily. The premature labor series has a value on the day of delivery of 13.0 mg. for 24 hours, and the postmature group an average output of 11 mg. Moreover, the premature curve seems to fall more rapidly before the onset of labor than was the case in the postmature or normal. The latter two correlate well in NaPG concentrations.

Several instances of false labor have contributed data to the consideration of a decreasing progesterone concentration as a requirement for the onset of labor. Browne¹⁶

and also Hamblen⁶ reported the NaPG concentrations were usually quite low in those individuals who aborted. Of the NaPG assays obtained during false labor, it was usual to show a considerable decline from the pregnanediol values obtained earlier in the pregnancy. When the false labor ended, an increase in NaPG values followed. This seemed to hold whether or not bleeding ensued, and whether or not there was evidence of toxemia.

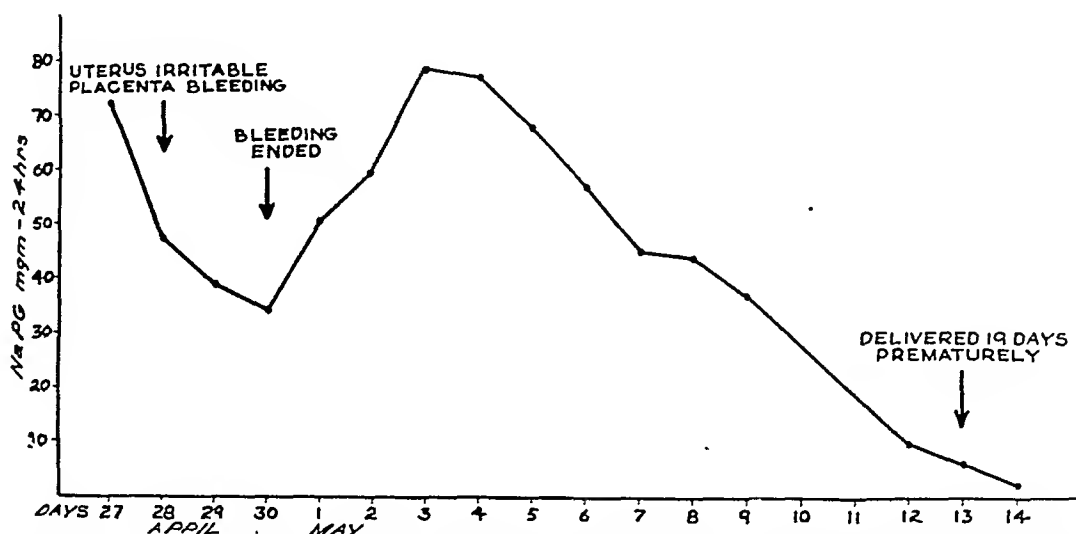


Fig. 6.—Pregnanediol excretion during placenta disorder. Premature partial separation of the placenta attended by diminished NaPG output during bleeding phase, with recovery but eventual premature delivery.

Fig. 6 illustrates the case of a 21-year-old para ii, gravida iii, weighing 58 kilograms, who was Rh negative, and was admitted at 35 weeks of pregnancy because of bleeding and a threat of premature labor. During the first few days in the hospital while at bed rest, there was a continuation of bleeding for three days, during which time the uterus showed an increase in tonus and irritability. The bleeding ceased by the fourth hospital day, contractions were less perceptible, and the NaPG output recovered returned to even higher levels than found on admission. Shortly thereafter, a progressive fall in the level continued unchecked until labor ensued nineteen days prematurely. Labor began when the patient excreted about 10 mg. of NaPG in the 24-hour period. Pregnanediol values during the early postpartum period were comparable to those of the average spontaneous delivery.

Discussion

Of the findings, one of the most significant is that the NaPG drop preceding the onset of labor occurs similarly in term, postmature, and premature groups. The decrease in output is approximately of the same range in each of the three categories. This would support a positive correlation between an extensive fall of conjugated pregnanediol and the onset of labor. Moreover, the relative similarity of the results from more than a hundred prelabor patients for NaPG values, when the glucuronic acid titration method was employed, strongly suggests that there may be a marked drop in available progesterone preceding the onset of normal labor. Since this was not clearly reflected in determinations made by earlier methods, and since all the techniques can measure substances other than pregnanediol, it is possible that the differences are inherent in the method. For example, a relatively small component of the assays recorded as NaPG are due to nonpregnanediol substances, namely, androgens. The estrogens are almost completely removed by the method of

extraction. The small proportion of the androgen component reflected by the titrimetric method values is probably not appreciably greater than 8 per cent of the total. After parturition, when the values recovered are in the 3 to 5 mg. range, androgens may compose a somewhat larger proportion. Moreover, this component is relatively constant and does not significantly affect the declining pregnanediol values seen immediately prior to labor. One investigator,⁷ using the glucuronic acid method, suggested by a few observations that relatively low pregnanediol assays occurred immediately before labor in some cases. From the rapid decline of NaPG preceding normal labor, it is probable that very little progesterone is available at the onset of labor.

Conclusion

The onset of labor is preceded for several days by a marked decline in the excretion of urinary sodium pregnanediol glucuronide. These declines are greater than any previously recorded. The difference from prior observations is attributed to the method and number of observations. It seems probable that progesterone production is diminished during the phase of decreasing NaPG values. It is implied that the concentration of progesterone available at the onset of labor is insufficient to maintain and continue pregnancy.

These assays were carried out with the faithful technical assistance of Mrs. Virginia Sutton.

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INCREASED EXCRETION OF PREGNANEDIOL IN PREGNANCY FROM DIETHYLSTILBESTROL WITH SPECIAL REFERENCE TO THE PREVENTION OF LATE PREGNANCY ACCIDENTS

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BEFORE reporting the effect of diethylstilbestrol upon the urinary excretion of pregnanediol in pregnancy, a brief résumé of the findings which led to this investigation is in order.

Evidence for a progressive deficiency of the placental steroid hormones before and during late pregnancy accidents has been a consistent finding in 50 women thus far followed by repeated analyses for the urinary products of estrogen and progesterone metabolism.¹⁻⁵ These included cases of premature delivery and intrauterine deaths, as well as pre-eclampsia (of varying degrees of severity) and eclampsia. Twenty-one of the women were diabetic, and in this group accidents involving death of the fetus predominated. Attempts at the definitive therapy of toxemia with estrogen and progesterone yielded only temporary alleviation of the hormonal deficiency and clinical signs.^{3, 4} Preventive therapy with estrogen and progesterone has been tried by us¹ and, at our instigation, in a fairly large series of diabetic patients⁶ with improved results, particularly as regards a reduction in fetal mortality in diabetics. We now have evidence⁵ that abnormalities in the production and metabolism of the placental steroids may have their incipience in the second trimester, indicating that truly preventive measures should be started as early as the sixteenth to eighteenth week. Replacement therapy over prolonged periods with the amounts of estrogen and progesterone indicated in pregnancy is still impossible. For this reason some means of stimulating the placental secretion of the steroid hormones has appeared to offer a more practical and physiologic approach. Administration of chorionic gonadotrophin is contraindicated because of the fact that the majority of these patients already have an excess of this hormone in the circulation² and seem to be unable to utilize it adequately for the production of placental steroids.^{2, 5}

In normal pregnancy, the rate of estrogen and progesterone secretion reaches a peak at about the thirty-eighth week and rapidly declines from then until parturition.⁷ The picture in late pregnancy toxemia and its associated accidents, therefore, may be considered one of premature decadence of placental secretion. A clearer understanding of the physiologic processes involved in the production of estrogen and progesterone has evolved from our studies of estrogen metabolism in women. From these it has been deduced

(1) that progesterone facilitates the metabolic conversion of the estrogens and hence depresses their rate of inactivation, (2) that estrogen inactivation products play an important role in the stimulation of sex steroid secretion,⁷⁻⁹ and (3) that the production of progesterone during the luteal phase of the menstrual cycle and around the thirty-eighth week of normal pregnancy is sufficient to reduce estrogen inactivation to such an extent as to remove the stimulus for sex steroid secretion.^{7, 10} The regression of the corpus luteum in the ovarian cycle, and the reduction of the placental steroid hormones during the last weeks of normal pregnancy may readily be explained on this basis. It has accordingly been proposed⁵ that the administration, during the middle months of pregnancy, of larger amounts of estrogenic material than could be metabolized by the available progesterone might supply a sufficient concentration of inactivation products to forestall any incipient premature deficiency of estrogen and progesterone. There was reason to suppose that diethylstilbestrol, as well as being inexpensive and effective by mouth, might be a more useful therapeutic agent for this particular purpose than the naturally occurring estrogens. Experimentally, it has been found to be 100 times as active as estrone in stimulating increased secretion and release of gonadotropic hormones from the pituitary of the intact rat.¹¹ It has also been shown by Pencharz¹² and others¹³ to have an augmentative effect upon the ovarian response of hypophysectomized rats to chorionic gonadotrophin, synergizing with this hormone to give pronounced enlargement of follicles and corpus luteum formation.

As a consequence of the above considerations and findings, we were led to investigate the therapeutic possibilities of diethylstilbestrol as a preventive measure against the premature decadence of placental secretion which appears to characterize late pregnancy toxemia and its associated accidents. In order to get some lead as to the proper dosage,* as well as to acquire more direct evidence for the progesterone stimulating properties of diethylstilbestrol in human pregnancy, we have done urinary pregnanediol determinations¹⁴ at weekly intervals on a pregnant diabetic woman during administration of the drug and during shorter periods when therapy was omitted.

Mrs. M. K., aged 36 years, gravida iii, had had pre-eclampsia and stillbirth in 1931, and pre-eclampsia with a living child in 1938. On August 22, 1944, when referred to one of us (D.H.) by her obstetrician, Dr. Samuel Sidell of Boston, because of sugar in the urine, she weighed 210 pounds. Her last menstrual period had been on May 26. Diabetes was diagnosed and controlled throughout the rest of pregnancy (together with a 10- to 15-pound loss of weight) by diet and protamine-zinc-insulin, 16 units daily to the twenty-seventh week, with a gradual increase to 30 units daily at term. Diethylstilbestrol orally was started on September 16, during the seventeenth week, and continued (with two interruptions as shown on the chart) through Jan. 29, 1945, the end of the thirty-fifth week. She had a normal pregnancy and spontaneously delivered a healthy 8-pound boy on February 28, four weeks after the cessation of therapy. There was no nausea at any time or other sign of toxicity from the drug.

*An approximation of the amount of diethylstilbestrol that might be required in pregnancy to stimulate progesterone secretion was made by comparing hormone excretion in the pregnant and nonpregnant woman and calculating on the basis of the dosage of the drug, which has been found by experience (G. V. S.) to prolong the cycle of nonpregnant women without inhibiting ovulation.

As shown on the chart, the urinary excretion of pregnanediol rose steadily while diethylstilbestrol was being taken, and dropped precipitously each time it was omitted. In normal pregnancy, fluctuations in the curve of pregnanediol excretion are observed, but the fact that this patient showed none while the drug was being taken, and that the three drops coincided with omissions of therapy, provides fairly conclusive evidence that diethylstilbestrol was responsible for the steady rise in pregnanediol excretion, presumably as a result of

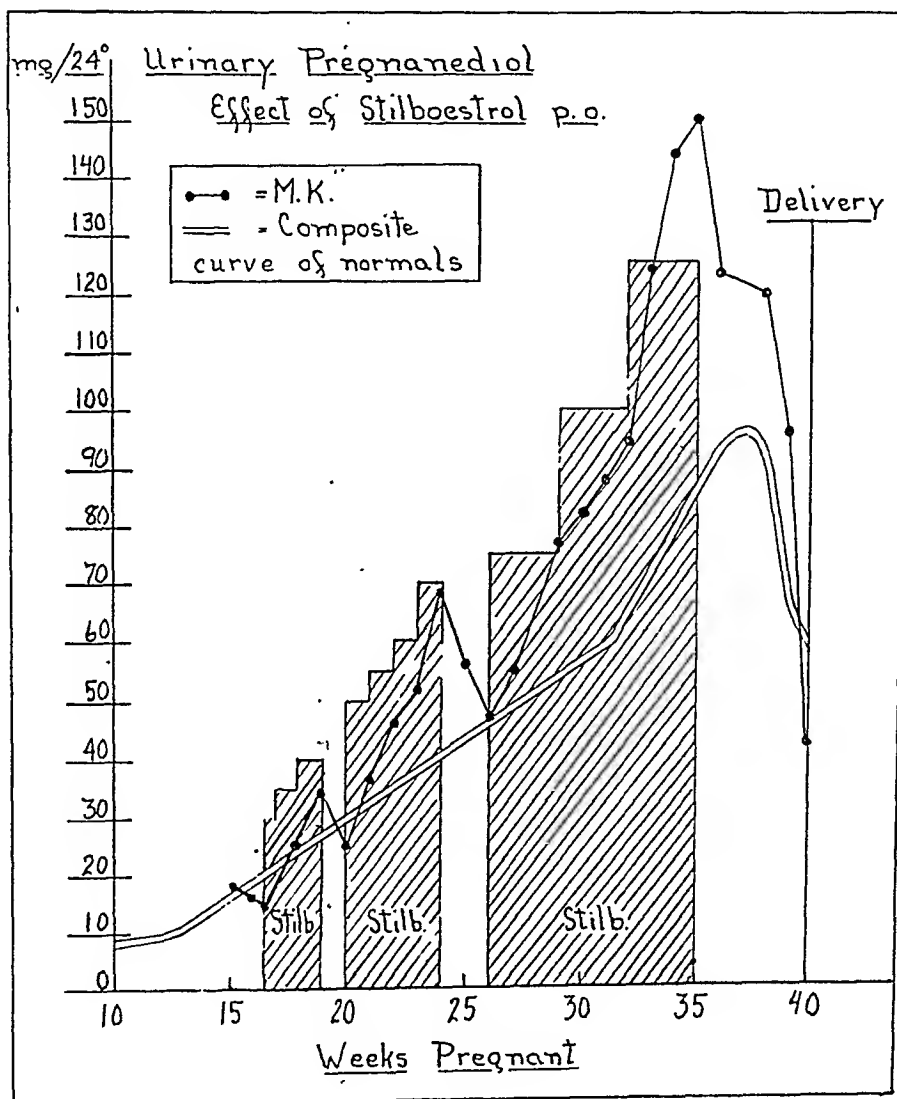


Fig. 1.

progesterone stimulation. The composite curve of normal values presented in the chart is compiled from our figures^{1, 2, 7} and those of Venning.¹⁵ The highest individual value that we have ever observed is 120 mg., whereas Venning reports none over 100. At the thirty-fifth week, after taking 125 mg. of diethylstilbestrol daily for 3 weeks, Mrs. M. K. excreted 150 mg. of pregnanediol in 24 hours. It is possible that 3 weeks of such large dosages constituted excessive therapy.

The amount and partition of estrogens were also determined in these urines, but interpretation of the results is difficult, since it is impossible to know how much of the excreted hormone was of endogenous origin, and how much derived from diethylstilbestrol. The values suggest that an increased secretion of estrogen was stimulated, and there is good evidence that the rate of estrogen inactivation was depressed during the periods of treatment, probably an indirect effect due to the increase in progesterone.

On the basis of these findings, we are recommending the following regime for the prevention of accidents in late pregnancy: diethylstilbestrol by mouth starting at the beginning of the sixteenth week with 30 mg. daily, and increasing the daily dose by 5 mg. at weekly intervals through the thirty-fifth week. For this purpose, 25 mg. tablets* may be supplemented by 5 mg. tablets to give the correct dosage. The progesterone stimulating properties of diethylstilbestrol make it an equally logical agent for the prevention of accidents in early pregnancy.† For patients in whom accidents are likely to occur before the fifth month, we are recommending 5 mg. daily starting 2 weeks after the last missed period, i.e., at the start of the seventh week of gestation, with 5 mg. increases in the daily dose at 2-week intervals to the sixteenth week and at weekly intervals thereafter. Therapy with diethylstilbestrol according to these specifications, for patients with repeated accidents in pregnancy, is now being tried by a number of individuals throughout the country and the results reported to us. We would appreciate case reports from any others stimulated by this publication to try it. In this way sufficient data should be collected in a relatively short time to be of statistical significance. The results to date are promising, and there has been no evidence of harmful effects.‡

Summary

A brief résumé is presented of the previously published findings which led to the hypothesis that the premature deficiency in the production of estrogen and progesterone characteristic of accidents in late pregnancy might be prevented by the oral administration of diethylstilbestrol.

The effect of this compound upon the urinary excretion of pregnanediol by a pregnant diabetic woman with a bad obstetric history has been investigated. The results provide good evidence that this synthetic estrogen stimulates progesterone secretion in human pregnancy.

A regime of stilbestrol administration by mouth is proposed as a preventive measure to be tried in cases with a history of repeated accidents in preg-

*Supplied by E. R. Squibb & Sons.

†Immediate relief of uterine contractions in threatened abortion and premature delivery has been observed by Karnaky¹⁶ as a result of the injection into the anterior lip of the cervix of large amounts of diethylstilbestrol. This author reports good results with the use of the drug both as definitive and preventive treatment of abortion and premature delivery, and suggests various possibilities as to its mode of action. Although our findings indicate that diethylstilbestrol stimulates progesterone secretion, it hardly seems possible that this effect would be an immediate result of local injection. We wonder if Karnaky's observations may not be due to some reflex nervous reaction, and if oil alone, so administered, might not elicit the same response.

‡Dr. John O. Haman of San Francisco performed liver function tests throughout therapy and for 6 weeks post partum on a woman treated by this regime, except that diethylstilbestrol was continued to term and the patient delivered by cesarean section. There was no evidence of liver damage. Urinary pregnanediol was also followed and rose steadily. This woman had had severe pre-eclampsia in a previous pregnancy with "resultant kidney damage." There was no toxemia in this pregnancy and the infant is living and well. "Excessive oozing" was noted at delivery and may well have been due to the drug. It has not occurred in patients who were allowed to deliver spontaneously 2 to 4 weeks after the last diethylstilbestrol.

nancy which may be referable to progesterone deficiency, namely, abortion, premature delivery, pre-eclampsia, eclampsia, or intrauterine death.

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LATE COMPLICATIONS OF THE WATKINS INTERPOSITION OPERATION*

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WATKINS, of Chicago, first did the interposition operation as we know the procedure, in December, 1899. His operation has been widely used since its inception. Today, however, one gathers the impression that the ordinary bladder advancement, the Manchester-Fothergill operation, and vaginal hysterectomy are gradually replacing the interposition. This is probably due to the Watkins operation causing a distortion of pelvic anatomy.¹

If our limited experience is an index of what may follow this procedure, not to mention what others must have seen but not recorded, we have a serious indictment of the operation. For those who continue to employ this operation, a consideration of late complications is in order. The interposition operation has held little appeal for us, consequently our series is negligible. The complications encountered have come under our care, though the operations were done elsewhere.

Carcinoma of the Corpus Uteri

McGlinn,² in 1927, reported a case of carcinoma of the uterine body occurring two years after he had done a Watkins operation. Dr. McGlinn stated then that he had been unable to find other reports of such a complication. Bissel, in a discussion of McGlinn's paper, stated that he had encountered two such cases; while Corvese³ two years later added another report, making four in all. We are, herewith, adding another case to the list, although we are certain this does not represent the incidence of such complications.

Mrs. M. B., aged 58 years, was operated upon by another surgeon two years previously. At that time she had a diagnostic curettage and a Watkins interposition operation done. About sixteen months after this operation she began to have recurrent episodes of slight vaginal bleeding. The patient consulted no one until the bleeding was constant, or eight months later, April 1, 1944. She was admitted to Chestnut Hill Hospital April 13, 1944, and on April 15, 1944, a diagnostic curettage was done with much difficulty. The interposition operation had been well done. The uterine sound was introduced with difficulty at a right angle to the posterior vaginal wall. Depth was three inches (6.6 cm.). A malleable curet was likewise introduced, bringing forth copious material which proved to be adenocarcinoma Grade II of the corpus.

Since McGlinn had attempted in his case to free the uterus from below and found it impossible, we chose the abdominal route as he did. On April 17, 1944, the patient was operated upon under spinal anesthesia. A retention catheter was first placed in the bladder and connected to an irrigation flask containing methylene blue and water. A two-way valve allowed the bladder to be filled and drained at our request, permitting better visualization and demonstration of landmarks. As it turned out, this simple procedure helped us greatly to keep out of the bladder.

*Read at a meeting of the Philadelphia Obstetrical Society, April 5, 1945.

We found the uterus firmly adherent under the pubic arch, deep in the pelvis, and completely covered over its posterior wall by bladder. No line of cleavage could be found, necessitating sharp dissection throughout. After the bladder had been freed from the uterus, the corpus was sharply dissected off the vaginal wall. Our patient was overweight. This added to the technical difficulty. In this particular phase of the operation, we opened the anterior vaginal wall from the urethral meatus to the cervix. Unlike McGlinn, we did not drain this area, but closed it from above. The lateral dissection of the tubes, ovaries, meters, and uterine arteries was without incident and seemed almost a minor procedure compared with the complete hysterectomy.

The entire operation was most difficult. If all gynecologists were called on to treat a corpus malignancy after a Watkins operation had been done, I am sure the interposition technique would no longer be used.

The patient made an uneventful recovery. She has a bladder capacity of 24 ounces, with occasional lapses of muscular control, as one would expect.

Phaneuf⁴ states that he has had to do only one panhysterectomy after the Watkins operation and, technically, it was difficult.

Pregnancy

It is apparent that this operation is indicated after the menopause because of the dangers when pregnancy follows. There are a number of cases reported in which the interposition operation was done without tubal ligation during the childbearing period. Practically all patients aborted or went on to term and cesarean section. Some of these patients have worn retention catheters from the eighth week on, however. In spite of this, one is able to find series of cases where the operation with and without sterilization has been done. In 1935 we⁵ reported a death resulting from a Watkins operation and sterilization. The surgeon in this instance had ligated and cut the tube on one side and the round ligament on the other side. The patient lived in a remote section of this country, far from medical attention. Her urethral obstruction due to pregnancy was complete, so that she developed a gangrenous bladder which had ruptured when we saw her.

Reduced Bladder Capacity

Recently there came to us a patient, Mrs. A. G., complaining of frequency of urination. Unless she restricted fluids to a bare minimum, it was necessary for her to void every hour. History revealed that three years previously, at the age of 39, a Watkins operation and sterilization was done for cystocele and slight prolapse. Following this, she complained of frequency only. Repeated urinalyses were negative. This complaint was more noticeable in the week previous to menses. Finally, she was castrated with deep x-ray. There followed only slight improvement. When we saw the patient, she was a miserable woman from this one complaint.

Pelvic examination revealed a well-interposed symmetrical uterus that was quite firm, but slightly larger than normal for a woman of her age, and not atrophic as one would expect in a castrate. On Jan. 29, 1944, we had Dr. Lowrain McCrea cystoscope the patient. This was his report: "The bladder capacity was markedly decreased; only 100 c.c. could be introduced. The floor of the bladder was markedly elevated, and the ureteral orifices congested. I

believe Mrs. G's symptoms are due purely to a mechanical reason caused by the uterus being pushed beneath the bladder. There is a question in my mind as to how much hydronephrosis has developed as a result of compression of the ureteral orifices. She does not appear to have any kidney deficiencies, nor does she have any pus and debris within the bladder. However, there is such a possibility if the bladder is left in such a position over a long period of time."

Up to this writing, the patient has refused to have the uterus removed per vaginam, vaginal hysterectomy being the only solution we see for this complaint.

Conclusions

1. The Watkins interposition operation, notwithstanding its complete distortion of pelvic anatomy, continues to find some advocates.
2. The Watkins interposition operation may be attended by serious complications when done in the childbearing period or after the menopause.
3. The ordinary bladder advancement operation, the Manchester-Fothergill technique, or vaginal hysterectomy should offer enough choice of procedure in cases where the Watkins operation formerly has been used.

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GERMANTOWN PROFESSIONAL BUILDING

Discussion:

DR. LOWRAIN E. MCCREA.—It was with considerable pleasure that I accepted the invitation to comment on Dr. Beecham's paper. However, I am a urologist, not a gynecologist, and I cannot tell the advantages or disadvantages, the indications or contraindications to this particular operation from a gynecologic standpoint. From a urologic standpoint, I can say that the disadvantages and the contraindications far outweigh the indications and the advantages. Let us forget about pregnancy and uterine carcinomatous infiltrations that you men are accustomed to handle, but look at it from the urologic standpoint. This operation is usually done in middle life or past middle life in the majority of instances. Sometimes it is done in the childbearing period. You would think that the fixation of the uterus beneath the bladder would be a far cry from the hydronephrosis, pyonephrosis, and pyuria that we see does exist. There are several definite changes that occur in the urinary tract following this operation. It has been my privilege to see three instances, all of them assuming the same proportions and the same end results. One thing that does occur is the formation of a cul-de-sac in the posterior portion of the bladder back of the trigone as the floor of the bladder is elevated in the new position. As a result of the elevation and compression of the ureter, hydroureter, hydronephrosis, or pyonephrosis occurs. At the same time, increasing bladder retention, nitrogen retention, and occasionally uremia develop. I have three slides: the first, a copy of the Watkins original operation, showing the elevation of the bladder by the operation. The second is an artist's conception of an actual case, showing position of the individual ureter lying on the outside of the elevated trigone, a deep recess in the lateral aspect of the bladder and the dome-shaped elevation of the trigone and floor of the bladder. The third is a urogram showing a bilateral hydronephrosis, marked decrease of the urinary output on the

left, a marked hydronephrosis on the right. The patient presented symptoms of uremia. After observing these changes in the urinary tract, I cannot, from the urologic standpoint, agree with the principles of the operation.

I think there is proof from the urologic standpoint that the procedure of Watkins interposition is a cause of an increased mortality among individuals whose life would otherwise not be shortened were it not for such a surgical procedure.

DR. PENDLETON TOMPKINS.—Since it is difficult to perform a hysterectomy for carcinoma of the fundus after a Watkins operation, would you consider the use of radium and x-ray irradiation? An objection is sure to be raised to this suggestion on the grounds that the position of the cervix and interposed fundus make it impossible to insert radium into the uterine cavity in the usual way. This is true. However, it is no great feat to expose the fundus which now lies beneath the urethra, to enter the uterine cavity through the fundus, and to insert the radium from that end of the uterus. If this is done, the bladder and urethra will be protected from excessive radium irradiation by the thickness of the uterine wall. X-ray treatment may be administered in the usual manner, with the addition of the "vaginal cone technique" if that seems desirable.

DR. WILLIAM R. NICHOLSON.—I have used the Watkins a great many times, and I maintain an operator should be able to distinguish between the round ligament and the tube in sterilization. Of course, when one meets an advanced case of carcinoma of the fundus, x-ray and radium is the proper treatment, but I still feel that the Watkins operation is good if used in suitable cases. No one should think of using it in the childbearing period unless the patient is sterilized, but in elderly women with a third degree prolapse the Watkins operation meets the indications, in my opinion.

DR. ADRIAN VOEGELIN.—May I say a few words in defense of an operation I have favored for many years, particularly for large cystoceles. All operations have occasional failures, and there is a possibility of a woman developing a fundal carcinoma after any sort of plastic. Admittedly, there will be considerable difficulty in undoing a Watkins.

I feel that the operation has a definite field in the case of a medium-sized or slightly smaller uterus.

Concerning the subsequent pregnancy, may I observe that a good gynecologist should be able to differentiate between a round ligament and a Fallopian tube.

Frankly, I have rarely encountered urinary complications, and then only temporary ones due possibly to the fact that the base of the bladder is well mobilized before anchoring the fundus to the fascia on each side under the pubic arch.

I failed to mention that, in my practice, amputation of the cervix is almost always done. This helps to approximate the cardinal ligaments as well as preventing the bougie-like action of an elongated cervix in descending to a lower level.

DR. BEECHAM (Closing).—We need add nothing to what Dr. McCrea has demonstrated so graphically. Most of the discussion has been around the small uterus, or as the textbooks put it, "the proper sized uterus." Therein lies a wide range of choice and, individualized as any surgeon is bound to be, accounts for the reduced bladder capacity.

Dr. Nicholson, as others, feels the Watkins is indicated in suitable cases. The literature gives no clue as to what constitutes a suitable case.

In my opinion the Watkins is an easy operation to correct a cystocele, but may produce many postoperative complications. The desired plastic result can be obtained by employing less dangerous procedures.

THE FETAL MORTALITY IN WOMEN DURING THE PREDIABETIC PERIOD

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THE abnormally high fetal and neonatal mortality of diabetic mothers has been a well-known phenomenon. Some observers have thought that this condition also obtained among children born to these mothers long before the diabetes became manifest. Miller, Hurwitz, and Kuder² reported an unusually high fatality rate even twenty years before the onset of diabetes. This somewhat startling observation prompted us to analyze the prediabetic fetal and neonatal mortality among women attending the Metabolic Clinic of the Mount Sinai Hospital.

The data relevant to this study were obtained by direct interview of two hundred married diabetic mothers. Their childbearing period occurred within the normal range of time, 83 per cent having had children before the age of thirty-one. Although the onset of diabetes developed at a mean age of 45.7 years, almost half, or 94 patients, first noted diabetes before the forty-fifth year.

TABLE I. FETAL AND NEONATAL MORTALITY IN PREDIABETIC WOMEN

	TOTAL BIRTHS	TOTAL STILL- BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	STILL- BIRTHS AND NEONATAL FATALITY
1-5 yr. before onset	39	3	3	6	15.4%
6-10 yr.	67	0	1	1	1.5%
11-15 yr.	106	5	4	9	8.5%
16-20 yr.	107	1	2	3	2.8%
21 or more yr.	307	12	7	19	6.2%
1 to 20 yr. period	319	9	10	19	6.0%
Entire series	626	21	17	38	6.1%

Table I summarizes the data with regard to fatalities by five-year periods prior to the onset of diabetes. A total of 626 children were born, including 21 stillbirths and 17 neonatal deaths, which yielded a total fatality rate of 6.1 per cent. Fetal and neonatal fatalities occurred in only 26 of the patients. The other 174 experienced no fetal or neonatal mortality at all. The average age of onset of diabetes of women with no fatalities was 45.2 years, and for those with fatalities, 48.9 years.

Three of the 26 women who had fatalities contributed 10 of the 38 deaths, or approximately one-fourth of them. In one instance, three fatalities occurred over forty years before the onset of diabetes. The second patient had marked hypertension, together with diabetes which developed at the age of forty. The third patient who contributed four fatalities, all twenty years before the diabetes was manifest, was a colored woman with syphilis.

Our fetal fatality rate of 6.1 per cent in prediabetic women resembled the figures cited by others for normal women. Miller, Hurwitz, and Kuder,² referring to a general series of 3,079 nondiabetic births at the New Haven Hospital, cited a total fetal mortality of 5.4 per cent. In a control group of 398 infants born to nondiabetic women comparable in age to the diabetic patients, our fatality rate was 3.01 per cent. In a subsequent study Miller⁴ reported a fetal mortality of 2 per cent in a control group of nondiabetic women. White³ cited a comparable figure of 3.4 per cent based on 600 nondiabetic cases delivered at the Faulkner Hospital, and a rate of 6 per cent for nondiabetic women at the Johns Hopkins Hospital.

Among our patients the twenty-year period immediately prior to the onset of diabetes, in which approximately half the births took place, was characterized by a total mortality rate of 6.0 per cent. A rate of 6.2 per cent was obtained for the prediabetic period of over twenty years. A significantly increased rate, 15.4 per cent was noted, however, during the first five-year period immediately preceding the onset of diabetes. Inability to determine the exact date of onset of diabetes probably led to the inclusion of instances of existing diabetes in this five-year period. The heightened mortality rate noted for this span of time cannot be interpreted wholly as a prediabetic phenomenon, since it probably represents diabetic conditions in part. Except for this first period, Table I displays no special trend in fatality rate for the other fifteen years preceding the onset of diabetes.

White³ cited a stillbirth mortality of 17 per cent prior to the onset of diabetes. Miller and his associates reported an even higher figure of 35.4 per cent among 79 children born in the first five-year prediabetic period. In their series of 252 children born during the entire twenty-year prediabetic period, there were 50 deaths, constituting a fatality rate of 19.8 per cent. This is approximately three times higher than that for our series in the same period. The disparity may be accounted for by the difference in age of onset of diabetes which in our series was 45.7 years compared with 34 years in theirs. Figures given in a later report by Miller⁴ based on women whose age at onset of diabetes was forty years, more closely resemble our findings. He found a rate of 15.8 per cent for the fifteen-year period prior to the onset of diabetes, and a rate of 6.0 per cent for the period sixteen years or more.

Relation of Fatalities to the Use of Insulin

Fifty-nine women did not require insulin in contrast to 141 whose diabetes was severe enough to warrant its need. Table II indicates that in the prediabetic state mothers who were

TABLE II. USE OF INSULIN AND FETAL MORTALITY

		NO. OF BIRTHS	NO. OF STILL- BIRTHS	NO. OF NEONATAL DEATHS	TOTAL FATALITY
Noninsulin patients	59	179	5	7	6.8%
Insulin patients	141	447	16	10	5.8%

destined to have severe diabetes requiring the use of insulin, had a fetal mortality rate no greater than those whose diabetes turned out to be relatively mild.

Abortions and Miscarriages

Miscarriages and abortions occur with relatively greater frequency in diabetic women after the onset of their illness. One hundred ten patients reported no fatalities, miscarriages, or abortions in the prediabetic period. The others sustained 88 spontaneous abortions in addition to fetal fatalities. On the basis of 714 pregnancies among the 200 women, the spontaneous abortion rate was 12.3 per cent. The corresponding figure for the general population reported by White³ was 11 per cent for "miscarriages or abortions."

TABLE III. USE OF INSULIN AND SPONTANEOUS ABORTIONS

	NO. OF WOMEN	TOTAL NO. OF PREGNANCIES	TOTAL NO. OF ABORTIONS	PER CENT ABORTIONS
Noninsulin patients	59	192	13	6.8
Insulin patients	141	522	75	14.4
Total	200	714	88	12.3

Table III presents the data in relation to the use of insulin. The women destined to have a moderate or severe diabetes requiring insulin had a higher percentage of abortions than the milder cases, the rates being 14.4 per cent and 6.8 per cent respectively. No such difference was noted in fetal and neonatal mortality with respect to the potential severity of diabetes.

Summary

Two hundred diabetic women gave birth to 626 children during their pre-diabetic years. The total infant fatality rate (stillbirths and deaths within ten days after birth), was 6.1 per cent. The corresponding rate for nondiabetic women as given by others ranged from 2 to 6 per cent.

The fetal fatality rate for the first five years preceeding the onset of recognized diabetes was 15.4 per cent. The first five-year prediabetic period revealed an increased fetal and neonatal mortality but the preceeding fifteen years was *not* characterized by such a tendency. The total rate for the entire twenty-year prediabetic period did not differ significantly from normal. The rate for the total twenty-year prediabetic period was about the same as that for the period of over twenty years, namely, 6 per cent.

The stillbirth and neonatal fatality rate among women who were destined to require insulin was not higher than among those who developed mild diabetes.

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AN UNUSUAL DECIDUAL REACTION IN THE CERVIX

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NORMALLY the mucous membrane of the cervix does not participate in the formation of the decidua.¹ However, rare instances of decidual reaction in the cervix have been described in association with polyps.² According to Novak,³ ectopic islands of decidual reaction may be observed in the cervix, the reaction being considered a metaplasia involving patches of mesenchymal cells which are sensitive to the hormones elaborated during pregnancy. Hennessy,⁴ in 1943, described a case in which there was an unusual type of decidual reaction in the cervix. In the course of a routine prenatal examination, a cervical lesion was observed which was suspected of being a malignant neoplasm. Biopsy revealed a very cellular tissue with marked decidual reaction between irregular glands which were scattered throughout.

The observation of an unusual variation of a rare pathologic entity warrants the reporting of the following case:

Case Report

A 23-year-old white primigravida was first seen in the prenatal clinic on July 20, 1944, by one of us (J.K.). Confinement date was estimated as January 31, 1945. Examination of the cervix revealed no polyps, erosions, or new growths. No unusual changes were observed on December 12, 1944, at which time the cervix was inspected during the completion of pelvic mensuration.

The prenatal course progressed uneventfully until 1:00 P.M. February 6, 1945, when the patient suddenly experienced a painless vaginal hemorrhage estimated at approximately one cupful of blood. She entered the hospital one hour later, at which time there were no evidences of shock, acute anemia, or toxemia of pregnancy. The blood pressure was 100 systolic, 70 diastolic. Examination of the abdomen revealed no areas of tenderness or rigidity; a full term fetus was found in the left occipito-anterior position, and the fetal heart was audible in the left lower quadrant. The sudden onset of painless vaginal bleeding with no gross evidence of premature separation of the placenta led to a presumptive diagnosis of placenta previa. The usual pre-examination precautions were taken. A compatible blood donor was obtained and preparations made for possible abdominal delivery. Vaginal examination revealed no evidence of placenta previa. The external os of the effacing cervix was found to be dilated one and a half fingers' breadth. The entire anterior lip of the cervix was replaced by an extremely soft, friable mass approximately 2 cm. thick at the portio. The gentlest manipulation of this area resulted in profuse bleeding necessitating the application of firm pressure in order to secure hemostasis. There were no polyps or erosions visible or palpable. The nature of the lesion was such that malignancy was strongly suspected. Further investigation was postponed pending parturition, the onset of which appeared to be imminent. Following a labor of five hours and fifty-five minutes, a living 7-pound, 9-ounce male infant was delivered by episiotomy and prophylactic low forceps at 6:55 A.M., February 7, 1945. Expulsion of the placenta and membranes at 7:00 A.M. was not followed by any undue bleeding. Immediate postpartum inspection of the cervix revealed neither lacerations nor bleeding. In obtaining a biopsy from the cervical lesion, the tissue was found to be more friable than anticipated. Hemostats crushed

through the extremely friable tissue exposing a raw surface from which dark blood spurted in multiple streams. It became necessary to insert figure of eight chromic catgut ligatures in order to secure hemostasis. The postpartum course was uneventful; the patient was discharged from the hospital on the seventh postpartum day.

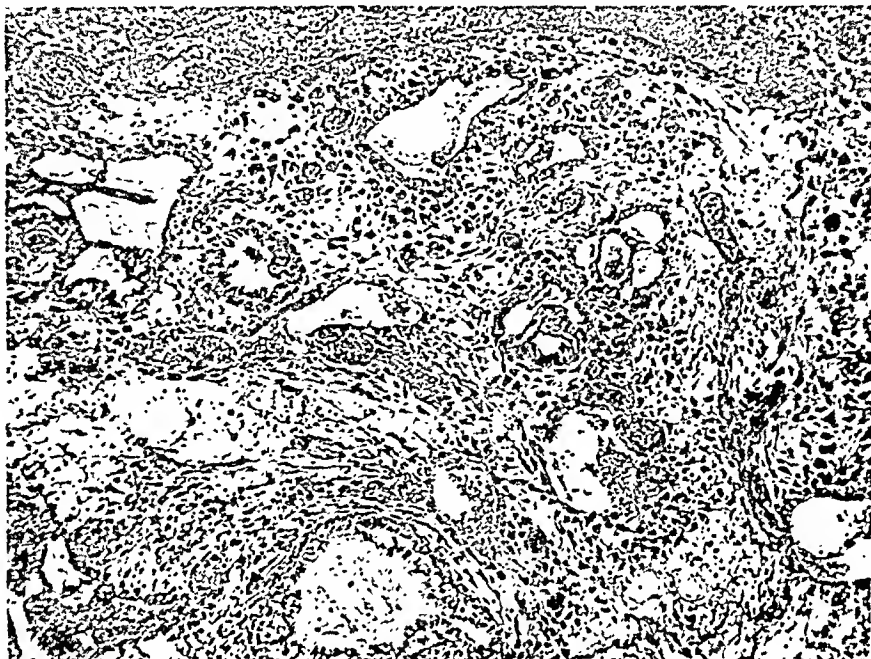


Fig. 1.—Low power; demonstrating cervical glands surrounded by papillary masses of pleomorphic decidua cells. (U. S. Army Medical Museum, Negative No. 85769.)

Pathologic Examination (L. H. D.).—

Gross: Small piece of red, friable tissue.

Microscopic: Sections were stained with hematoxylin and eosin. The tissue consists of papillary masses of decidua showing many areas of necrosis. (Fig. 1.) A few normal appearing cervical glands are scattered throughout. In the basilar portions, the decidua tissue has a mature appearance, but as the free edge is approached, the cells vary considerably in size and shape. Spindle-shaped, stellate-shaped, and polygonal cells are present. The cytoplasm is slightly granular for the most part, but in many of the cells it is vacuolated and sievelike. Variation in staining of the cytoplasm is marked, varying from a pale pink to bluish-purple in the advancing portions of the mass. In many instances the cells are fused together. The nuclei are ovoid, vesiculated, and, in some, a prominent nucleolus is seen. Some cells are binucleated, and in these the perinuclear cytoplasm is a light lavender color surrounded by a rim of deep blue-staining, more compact cytoplasm with the periphery being light lavender. Some areas contain a fairly large amount of stroma. In these areas the decidua type of cell is not numerous. However, a network of fibers is present between which a pink-staining, granular material is found. Neutrophils are scattered about, and in some areas there is marked necrosis. The tissue is extremely vascular, many large blood-filled spaces of the cavernous and hemangiomatous types are seen. In one of the larger spaces, a partially organized thrombus is present. The surfaces of the papillary masses are partially covered by epithelium which varies from a low cuboidal to a columnar type. Occasionally, this epithelium extends down into the crypts forming mature cervical glands. These crypts contain neutrophils and debris. Normal cervical tissue stroma is not present; only a few typical cervical glands are seen surrounded by decidua tissue.

Diagnosis.—Decidua reaction of the cervix.

Examination of the patient on March 8, 1945, four weeks post partum, revealed a firm cervix which was normal in all respects, except for a small erosion of the anterior lip.

There were no evidences of the lesion which had presented itself prior to delivery. The cervix had apparently undergone involution consistent with that of the fundus uteri. In view of the invasive potentialities of the decidual reaction, it was deemed advisable to biopsy the cervix to exclude a possible malignant neoplasm.

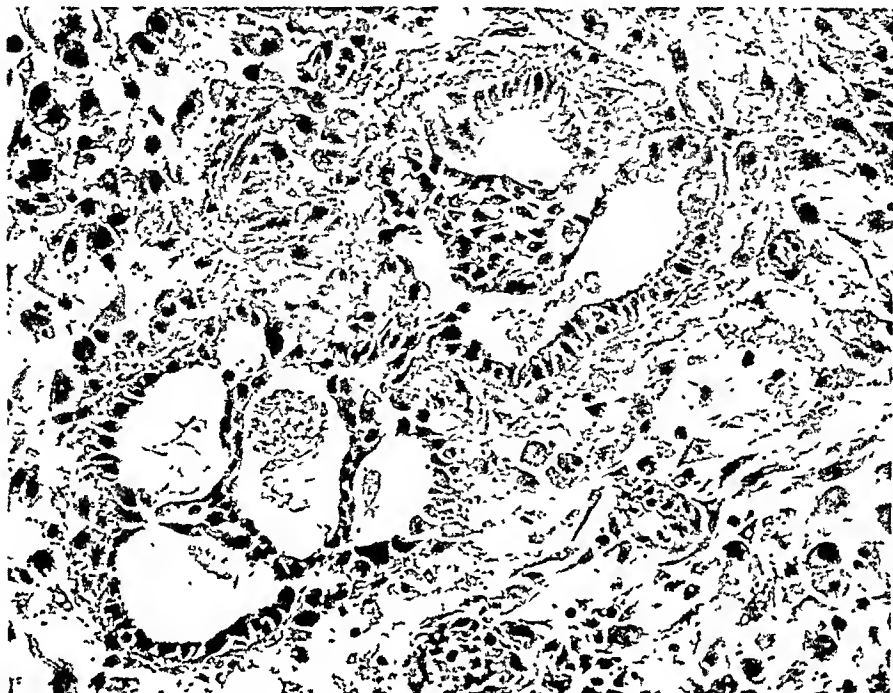


Fig. 2.—High power ($\times 400$). (U. S. Army Medical Museum, Negative No. 85770.)

Pathologic Report.—

Gross: A small piece of cervical tissue 3 mm. in the greatest diameter is present. The surface epithelium is composed of a few small brownish-gray areas where the mucosa is soft.

Microscopic: Sections of the tissue show the stratum mucosum of the squamous epithelium to be slightly thickened. Some vacuolization of the cells, pyknosis, and an infiltration of neutrophiles is present. There is a prolongation of the rete pegs into the compact, well-vascularized supporting stroma. A few lymphocytes, mononucleated cells, and an occasional neutrophile are scattered through the stroma. The transition from squamous epithelium to columnar epithelium is abrupt but obscured by ulceration, where the surface is covered by a small amount of fibrin and neutrophiles. Elsewhere the columnar epithelium is fairly well preserved. A few slightly dilated cervical glands are present in the supporting stroma. Some contain a pink-staining debris and neutrophiles. The subepithelial supporting stroma of this portion is densely infiltrated with plasma cells, lymphocytes, a few neutrophiles, and eosinophiles. More deeply, the reaction is less intense. There is good vascularization with some of the vessels showing a thickened media. There is no evidence of a decidual reaction or malignancy in this biopsy.

Discussion

Decidual reaction in the cervix is a rare occurrence. However, when seen it is usually associated with polyps. The above described case is unusual in that there were no polyps. Furthermore, microscopic examination of the biopsy suggests more than the ordinary type of decidual reaction. The marked histologic variations of the decidual cells seen at and below the free margins of the specimen, as contrasted with the more mature cell-type present at the site of amputation, indicates, we believe, an unusual degree of cellular activity. Also, the presence of cervical glands encompassed by pleomorphic decidual cells, plus the papillary-like architecture suggests invasive potentialities.

It is interesting to note that involution of the cervix as manifested by gross and microscopic return to a relatively normal state was apparently consistent with the progress of that process in the fundus uteri.

The investigation of the source of vaginal bleeding during pregnancy has rightfully been considered an obstetric dogma. Nevertheless, all too frequently it has been neglected or has been conducted in a haphazard manner. In many instances, a presumptive diagnosis of placenta previa based on history exclusively has resulted in unnecessarily subjecting a patient to the additional risks of abdominal delivery. A more discerning investigation might have revealed pathologic changes in the cervix as the basis of the bleeding.

The common teachings of "biopsy every suspicious lesion" cannot be emphasized too strongly. In the above described instance, the correct diagnosis would never have been made had this procedure not been employed.

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SUBACUTE BACTERIAL ENDOCARDITIS COMPLICATED BY PREGNANCY, SUCCESSFULLY TREATED WITH PENICILLIN*

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THE following report is the sixteenth case in a series of patients with subacute bacterial endocarditis treated with penicillin by Dr. Louis Katz at Michael Reese Hospital.

The patient, a 24-year-old gravida ii, para 0, entered the hospital Jan. 2, 1945, for a therapeutic abortion. The indication was rheumatic heart disease present since the age of 8 years and complicated by congestive failure at 13 years. She had been confined to Michael Reese Hospital for six months with this latter episode. During the three years following the failure, the patient had had minor attacks of fever and fleeting joint pains which had confined her to bed for two to four weeks at a time. In the past eight years her health had been good.

In May, 1943, Dr. Rubovits performed a therapeutic abortion when the patient was ten weeks pregnant, and advised against future pregnancies.

When admitted to the hospital in January, 1945, the patient gave a history of having had a cold for the past two weeks accompanied by backache, low-grade fever, nausea, and occasional tenderness in several of the digits.

The essential physical findings were: blood pressure 115/65; pulse, 100; and temperature, 100° F. The palpebral conjunctivae were pale; petechiae were not seen. The pharynx was slightly injected; the lungs were clear. The heart findings were those of a mitral stenosis and insufficiency and aortic insufficiency, with good cardiac reserve. The liver and spleen were not palpable. The pelvic findings were consistent with a twelve weeks' intrauterine gestation. On the outer border of the right foot there were two reddish areas which did not blanch on pressure and were slightly tender to palpation. The blood count revealed a hemoglobin of 10.2 grams (61 per cent), red blood count of 3.75, white blood count of 9,900; platelets were increased, and the sedimentation rate was 37 mm. per hour.

Subacute bacterial endocarditis was suspected, and blood for culture was obtained. The specimens obtained on Jan. 3 and Jan. 5, 1945, revealed *Streptococcus viridans*.

The abortion was, of course, contraindicated, and the patient was referred to Dr. Katz for treatment. The penicillin sensitivity of the patient's organism was determined in vitro and found to be good (0.01 unit per cubic centimeter). Dr. Katz felt that this indicated a good prognosis, if he could judge by past experience with this type of organism.

Penicillin was begun Jan. 10, 1945; 200,000 Oxford units were given daily in divided hourly doses (1 c.c. = 8,333 Oxford units). On January 13 (two and one-half days after the first injection of penicillin) the blood culture was negative. Repeated subsequent cultures were negative.

By the end of January, when the patient was about sixteen weeks pregnant, Dr. Rubovits presented to the obstetric staff the problem of whether or not to interrupt the pregnancy. After considerable pro-and-con discussion, every member voted to allow the pregnancy to go to term. However, by Feb. 13, 1945, after five weeks of penicillin treatment, Dr. Katz was not satisfied with the patient's progress. She continued to have new petechiae, although the blood cultures remained negative, and rectal temperatures were below 100° F. Comparison of the response of this patient with the others who had had a similarly sensitive strain of *Streptococcus viridans* was not favorable. This patient was pregnant; the others had not

*Presented, by invitation, at a meeting of the Chicago Gynecological Society, April 20, 1945.

been, and he felt that the pregnancy might be an unfavorable influence on the course of the disease; he therefore urged that it be terminated. Accordingly, on February 19, the patient was prepared for laparotomy.

When the abdomen was opened, the uterus was found to be enlarged to the size of an eighteen-week gestation, and several small subserous and intramural leiomyomas were encountered. Because of the latter lesion, a supracervical hysterectomy, rather than a hysterotomy, was performed. The postoperative course was uneventful. Penicillin therapy was continued until March 9 (two and one-half weeks postoperatively), completing eight weeks of treatment.

The sedimentation rate was determined on March 2, and on March 14, and found to be 12 and 11 mm. per hour, respectively. How much credit for this normal sedimentation rate can be assigned to the removal of a possibly harmful pregnancy on the course of the septicemia is not clear, because of the high sedimentation rates that normally occur in pregnancy.

The fetus was cultured after its removal from the uterus. The cord blood and liver were negative. The placenta revealed *Staphylococcus albus*. No streptococci were found. Incidentally, in this connection, it might be interesting to mention that one would expect to find a so-called sterile fetus when the mother's blood has become negative. Penicillin has been shown to pass through the placental barrier, and the penicillin level in the blood of the fetus is the same as that in the mother.

On March 14, 1945, five days after therapy had been discontinued, a new group of petechiae were noticed. The patient's temperature was 99.8° F, the sedimentation rates remained normal, and repeated blood cultures were negative; this was therefore considered to be a "sterile episode." The patient was discharged on March 18, 1945, nine days after penicillin had been discontinued. Her cardiac reserve was good, and she was considered to have recovered from subacute bacterial endocarditis.

How much influence the pregnancy actually had on the course of the disease cannot be answered. It is hoped that all pregnant women unfortunate enough to have subacute bacterial endocarditis may be carefully studied by a research group especially interested in this problem. Only in this way can we weigh the accumulated evidence and decide on our course of treatment in the future.

RUPTURE OF THE SPLEEN AS A COMPLICATION OF PREGNANCY*

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SPONTANEOUS rupture of the spleen, although reported in other cases, is a rare complication of pregnancy. Only twenty-two cases are reported in the literature. Because of the rarity, the difficulty in diagnosis, and the rapidity of death, most cases of rupture of the spleen are not recognized during life and are discovered only at postmortem examination. Early in pregnancy, the diagnosis is most often confused with ruptured ectopic pregnancy, and later with rupture of the uterus or extensive premature separation of the placenta.

The following case of rupture of the spleen serves to emphasize the rarity of this condition.

Case History.—The patient was a Negro woman, aged 30 years, gravida vi, para iii, who entered the hospital complaining of a severe frontal headache. She stated that for the past two months she had had edema of the lower extremities, chronic headache, fainting spells, and blurring of vision. A severe nocturia had been present during this time. The patient was in her thirty-sixth week of pregnancy.

The family history was noncontributory. The patient had been followed in the Medical Clinic of the Out-patient Department for the last three years, and had been treated for hypertensive heart disease. She had received antiluetic treatment intermittently for three years. However, for four months previous to admission, she did not receive any therapy. She had three children, all delivered spontaneously and without complications. In two subsequent pregnancies she was hospitalized with the same complaint as on this admission. Both resulted in premature stillbirth deliveries.

Physical Examination.—Temperature 99.8° F.; pulse, 100; respiration, 24; blood pressure, 230 systolic, 115 diastolic. On ophthalmoscopic examination, there was marked arterio-venous compression. There were fine moist râles in the bases of both lungs. The maximum impulse was in the fifth interspace in the left anterior axillary line. A soft blowing systolic murmur was heard in the mitral area, transmitted to the axilla; and over the pulmonic region, transmitted to the neck. The rhythm was regular, rate 100. Abdominal examination revealed cephalic presentation with the occiput to the right. The fetal heart tones were heard in the right lower quadrant. The heart rate was 140. The height of the fundus was 26 cm. There was moderate diastasis recti. On rectal examination, the cervix was thick, uneffaced, and about 1 cm. dilated. There was 1 plus pitting edema of the lower extremities.

Laboratory Examination.—Urine showed a trace of albumin on several occasions but no casts. Hemoglobin was 10 gm. per 100 c.c.; white blood count, 17,200; red blood count, 3.45 million. Nonprotein nitrogen, 28 mg. per cent; uric acid, 4.68 mg. per cent; creatinine 1.58 mg. per cent.

Course in Hospital.—The patient was placed on a regime consisting of 20 per cent glucose, and 10 per cent magnesium sulfate intravenously, sodium luminal for sedation, and strict bed rest. Under this routine the patient improved considerably. The edema of the extremities and the râles in the lungs disappeared. The blood pressure progressively decreased from 250 systolic to 140, and from 115 diastolic to 110. After one week, the patient's condition was greatly improved and she was permitted to sit up in a chair.

Approximately seventeen days after admission to the hospital the patient awakened at 5:00 A.M. screaming with pain. Examination at this time revealed moderate tenderness of the epigastrium but no spasm or rigidity. The blood pressure could not be obtained. The pulse was rapid and thready. Fetal heart tones were inaudible. The patient was given

*Research paper 581, Journal Series, University of Arkansas.

intravenous fluids, caffeine, and whole blood transfusions. The blood pressure rose to 90 systolic and 70 diastolic. Approximately one hour after onset of the acute pain, there was some distention of the upper abdomen and a definite fluid wave, and shifting dullness could be elicited.

A diagnosis of internal abdominal hemorrhage was made, and the patient was prepared for operation. However, before surgery could be performed, death occurred, seven hours following the onset of the severe abdominal pain.

Autopsy Report.—The chief pathologic findings in the case were in the abdominal cavity and in the heart. Approximately 1,500 c.c. of fresh blood and clots were present in the abdominal cavity. The spleen was surrounded by clotted blood, and it had an irregular tear 5.0 cm. in length on the anterior surface 1 cm. below the tip of the upper pole. The spleen weighed 410 grams. It was very soft and friable and reddish-purple in color. There was no evidence of an inflammatory reaction at the margin of the laceration. The pulp was extremely hemorrhagic. The lumen of the splenic vein was completely filled with a thrombus extending from the superior mesenteric vein to the hilus of the spleen. The splenic artery was patent grossly, however, on microscopic examination of the smaller branches at the hilus; it had a thrombus which was attached to the vessel wall.

The liver weighed 2,010 grams. It was softer in consistency than normal. Multiple delicate fibrous adhesions were present between the liver and diaphragm.

A well-developed, well-preserved fetus of approximately eight months gestation was present in the uterus. Myomata 1 to 2 cm. in diameter were present in the uterine wall.

The heart weighed 490 grams. The wall of the left ventricle measured 3 cm. and the right 4 mm. in thickness. The margin of the mitral valve was slightly thickened, and nodular and the chordae tendinae were slightly shorter than normal. The right ventricle was moderately dilated.

The kidneys were normal grossly. The basement membrane in a few of the glomeruli was slightly thickened. Only one arteriole was found with an abnormally thick wall.

Discussion

Shannon,¹ in 1940, collected from the literature twenty-one cases of spontaneous rupture of the spleen complicating pregnancy and added one of his own. Over 50 per cent of these cases have a history of trauma. There were six cases of rupture of an aneurysm of the splenic artery. No cases of splenic rupture have been reported since 1940. Thrombosis of the splenic vein has not been reported in any of the twenty-two cases of rupture of the spleen.

Thrombosis of the splenic vein is comparatively uncommon, except when it is associated with cirrhosis of the liver. Inflammatory lesions, such as ulcers of the stomach, pancreatitis, compression by tumors, twist of the pedicle of the spleen, are some of the etiological processes associated with splenic thrombosis. None of these was observed in this patient.

An increase in the volume of the spleen is known to follow periods of rest. It has been shown by several investigators²⁻⁴ that sodium amytal, pentobarbital sodium, and pentothal sodium may produce enlargement of the spleen which persists for several hours after the administration of the drugs. The systolic blood pressure of the patient being discussed decreased from 230 to 140 under therapy. The reduction of blood pressure and the stasis resulting from barbiturates would favor thrombosis of the splenic vein. The pressure of the uterus upward would tend also to aid the process of congestion. Although the patient was serologically positive, there was no histologic evidence of syphilis, and syphilis is not believed to have played any part in the pathology found. The findings in this case suggest that stasis may have contributed to thrombosis of the splenic vein. Brines,⁵ in a review of cases of rupture of the spleen in nonpregnant individuals, cites a case reported by Pringle in the *Irish Journal of Medical Science* in which antemortem thrombosis of the splenic artery and tuberculous splenitis were found.

Summary

A case of thrombosis of the splenic vessels with rupture of the spleen occurring during late pregnancy is reported. Only twenty-two other cases of splenic rupture occurring as a complication of pregnancy have been reported. The pathogenesis of this lesion is briefly discussed.

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American Obstetric Services

THE JOHNS HOPKINS HOSPITAL

Baltimore, Maryland

THE history of the Johns Hopkins Obstetrical Service spans half a century. At the time of its inception in 1895, prenatal care was unknown; the modern sphygmomanometer was yet to be invented and, since blood groups had not been discovered, transfusion was for the future. Furthermore, the vast majority of pregnant women did not enter a hospital for delivery—that was a fate reserved for the prostitute and the homeless poor.

When the Johns Hopkins Hospital opened its doors, May 16, 1889, no beds were allotted to maternity cases and no provisions were made for a home delivery service. Despite this, a few days later Dr. Howard A. Kelly was appointed Gynecologist and Obstetrician-in-Chief to the Hospital. No attempt was made to organize an obstetric service until the opening of the Medical School forced the issue several years later. Then the responsibility of initiating and administering an obstetric service was delegated by Dr. Kelly to a 29-year-old member of his gynecologic staff, John Whitridge Williams.

The home delivery service was begun eighteen months before the indoor hospital service. The first home delivery was the spontaneous birth of a white female infant on January 1, 1895; the mother's eighth child. The second patient was a severe cardiac who was phlebotomized and digitalized in her home by Dr. Williams, with Dr. Thayer, later destined to be a distinguished internist, as consultant. Contrary to modern practice, Dr. Williams induced labor with a silk bougie to relieve the patient's cardiac distress. Thirty-eight women were delivered in their homes the first year, and one hundred and twenty-five the second.

The first obstetric admission to the Hospital was on June 18, 1896, although the patient did not deliver until two months later. She was an unmarried Negro woman who was granted board and shelter in return for the service of allowing staff and students to practice palpation upon her. In the meantime, the second patient admitted delivered before her, July 29, 1896. She was also an unmarried Negro woman, as were all the hospital obstetric patients for several months. Even on this unhurried obstetric service (there were only sixteen deliveries in 1896) "B.O.A.'s"* occurred, as the third case history concisely states: "with two hard pains child was born. Delivered by head nurse as Dr. Dobbin was not on the ward." The first death occurred in the ninth patient who was admitted semicomatose with far-advanced nephritis. In many respects her treatment and study sounded quite modern; in other respects like the half century ago that it was. The patient was placed on a

*Born on arrival.

milk diet, given cream of tartar water, and infusion of digitalis. Since there was no improvement, a hot bath twice a day was prescribed. Delivery occurred, but still no improvement, so she was given subpectoral salt, jalap as a purge, hot packs, and pilocarpine hypodermically. Despite therapy, she died in uremia six weeks post partum. Of course, the history contains no mention of blood pressure readings, blood chemical studies, or kidney function tests. Frequently, the obstetrics practiced in the Clinic during these early years was extremely radical as judged by modern standards. Thus, many a history attests the fact that a favorite method of treating both eclampsia and placenta previa prior to 1910 was immediate and rapid manual dilatation of the cervix, version, and extraction.

Dr. Kelly recommended to the medical faculty as early as 1896 that Dr. Williams be made Professor of Obstetrics, but they did not accept the recommendation. Perhaps they thought Dr. Williams too young. At all events, when he was 33 years of age, in 1899, the Chairs of Gynecology and Obstetrics were divorced, and J. Whitridge Williams became Professor of Obstetrics in the University and Obstetrician-in-Chief to the Hospital, positions which he held with great eminence until his death in 1931.

Until 1923, the Department worked under the serious but not insuperable handicap of totally inadequate, makeshift quarters, consisting of two-thirds of the building originally designed for the general isolation ward of the Hospital. The bed capacity was very limited, and beds for private obstetric patients were nonexistent. There were only two small delivery rooms, all laparotomies being performed in the gynecologic operating room. Laboratory space was cramped.

In 1923, through the generosity of Lucy Wortham James, supplemented by funds from the General Education Board, a new building was erected. The architectural possibilities were somewhat circumscribed through the fact that it was necessary to construct it upon the site of two of the original buildings of the Hospital, which were so well built that it was deemed economical and expedient to utilize their foundations and even part of their walls. This new building, in the spirit of the old "Frauenklinik," housed both the Departments of Obstetrics and Gynecology, though they long remained entirely separate clinical, administrative, and scientific units.

The Woman's Clinic is a fireproof red brick, six-story structure which quite obviously was built with utility as the chief cornerstone. The sixth floor houses the gynecologic operating rooms and a bacteriologic laboratory used jointly by the two services, obstetrics and gynecology. On the fifth floor are the labor, delivery, and obstetric operating rooms. The fourth floor has eleven rooms and fifteen cubicles for private patients. These beds are shared by the two departments. In addition to a nursery, the fourth floor has laboratories and offices for the obstetric staff. Here there is a pathologic laboratory, where one could always find Dr. Williams in his vest and shirt sleeves, reaming and smoking a very strong pipe. In addition, there are chemical laboratories, photographic rooms, and animal quarters with space for endocrine research. One room is devoted to the stereoscopic equipment used in x-ray pelvimetry. The third floor is divided equally between obstetrics and gynecology for the

care of white ward patients, the west half being occupied by obstetrics, the east half by gynecology. On the obstetric side there are single rooms and two eight-bed wards with a total bed capacity of twenty-eight. The second floor, entirely given over to Negro patients, is simply a duplicate of the third. These two floors each have a main nursery with several small side rooms for isolation. The nurseries have large modern incubators. The first floor is devoted to the offices of the professors of obstetrics and gynecology, and to those of the head nurses. In addition, there is a large classroom whose walls are covered with the pictures of more than fifty of the medical worthies who transformed midwifery into the science of obstetrics. A very complete obstetric museum contains several hundred gross pathologic specimens, real and modeled pelves, as well as an historical collection of obstetric instruments.



Fig. 1.—Woman's Clinic, Johns Hopkins Hospital.

The Williams Obstetrical Library occupies a large room on the main hospital corridor. It contains several thousand volumes very carefully chosen. Among these we find complete files of the outstanding medical journals of the English, German, and French languages. The important textbooks and volumes on special obstetric and gynecologic subjects are on its shelves. Many books on medical historical subjects are to be found. A three-quarter portrait of Dr. Williams by the late Thomas Corner dominates the room.

Dr. Williams and his staff published a number of studies on all phases of obstetrics. Dr. J. Morris Slemans in the "Academic Aspects and Bibliography of John Whitridge Williams" lists 137 publications by Dr. Williams over a period of forty-two years. His main interests were contracted pelves, obstetric pathology, and obstetric teaching. Yet he wrote on many other topics such as syphilis in pregnancy, induction of labor, premature separation, pernicious

vomiting, prenatal care, sterilization, the toxemias, etc. Many of his associates, during the thirty-two years he occupied the professorial chair, contributed to the literature. They wrote on bacteriologic, chemical, historical, and clinical topics—among these we may mention: Welch bacillus puerperal infection, the normal and pathologic flora of the vagina, blood chemistry and the toxemias, arsenic in the placenta of the woman treated for syphilis during pregnancy, apnea and asphyxia neonatorum, and their relation to the inhalation anesthetics, the history of cesarean section, the imaginary accouchement by Ambroise Paré of a great sixteenth century French lady, induction of labor, postpartum hemorrhage, syphilis, etc. Following Dr. Williams' death in 1931, Dr. John M. Bergland was appointed acting professor until the present professor of obstetrics, Dr. Nicholson J. Eastman, was appointed in 1935. Dr. Eastman had been a member of Dr. Williams' staff from 1928-1931, before he went to Peiping as Professor of Obstetrics and Gynecology at the Rockefeller School there.

Since Dr. Eastman assumed the Professorship of Obstetrics, and Dr. Te Linde the Professorship of Gynecology, the two departments have become closely integrated. Thus, an internship on either service includes periods spent in both departments; similarly, in the higher brackets of the house staff this interchange is continued with the result that a man going through to the residency in either department receives thorough training, including major operating responsibility, in both fields. Likewise, the laboratories have been unified and much of the research in the clinic is carried out and published jointly by the two departments. Although investigative work was greatly curtailed because of the war, recent publications have included studies on vitamin K, sodium pentothal, contraception, the toxemias of pregnancy, twinning, rupture of the uterus, pregnanediol excretion, prolan assay, sperm physiology, etc.

Clinical research has been greatly facilitated by the use of the punch card. From the beginning of the clinic until January, 1936, all obstetric histories, both home and hospital, have been coded and transferred to a 40-column card. Since 1936 an 80-column card has been used. A full-time technician is employed in the coding, punching, and sorting of the obstetric histories. By now this represents a mass of clinical material. From the inception of the outside obstetric service in 1895 to its abandonment in 1940, there were 17,309 term and premature deliveries. From 1896 to 1945 there have been 39,343 hospital deliveries, so that 56,552 deliveries have been placed on punch cards up to January 1, 1945. At present, between 1,800 and 2,000 women are being delivered in the hospital annually, three-fourths being clinic patients.

The Hopkins is fortunate in that its ward service is equally divided numerically between white and Negro patients, for the latter group presents exaggerated pathologic obstetric states which are much less frequently found in the white. Rachitic pelvis, uterine fibroids, syphilis, and chronic hypertensive arteriolar disease are far more common and more marked in the Negro woman. The obstetric pathology is further increased through referrals to the Hopkins from nineteen State Health Department Clinics scattered throughout the length and breadth of Maryland. These clinics are conducted by local

physicians, health officers, or well-trained nurse midwives, and are visited monthly by a consulting senior staff member of the obstetric department. The abnormal cases are sorted out and referred to the Hopkins for observation, treatment, or delivery.

Emphasis is laid on postgraduate as well as undergraduate teaching. Staff rounds are held on Monday afternoon from two until three-thirty. At this time three or four cases, selected because of unusual interest, are presented by the resident staff and then discussed by the professor and other members of the senior staff. These rounds are also attended by obstetricians of the community, graduate nurses and medical students. One morning a week the Professors of Obstetrics and Pediatrics with their staffs make joint nursery rounds. On one afternoon, a dispensary consultation clinic is held. The prenatal clinic is conducted entirely by the house staff, but each week they select complicated and puzzling cases to present to the senior staff for discussion and guidance. Each Saturday morning at ten o'clock, the professor and staff make bedside rounds on every ward patient.

The undergraduate teaching in obstetrics is done in the second and third years of the medical school. During the final quarter of the second year the students receive ten introductory talks on obstetrics. Throughout the whole third year one hour a week is devoted to a lecture on either obstetrics or gynecology. For one full quarter of the third year, approximately eight weeks, the student devotes almost full time to obstetrics. Obstetric lectures, conferences, and ward rounds are held daily throughout the morning. In order to increase the mass of pathologic material, one of the rounds is conducted on the wards of the adjacent Sinai Hospital. In addition to classes, the students serve on the wards and in the delivery rooms. They conduct deliveries under rigid supervision and scrub for operations. Each ward admission is assigned to students in rotation, and the patients remain their responsibility until discharged. Students attend the prenatal clinic in small groups to learn palpation and pelvimetry. In addition manikin sessions are held two hours a week. This plan of concentrated obstetrics provides the students with the opportunity of attending small classes, fifteen to twenty each quarter, which compensates for the greatly increased burden it places upon the teaching staff; for the same curriculum must be repeated four times during the course of one academic year.

The house staff in obstetrics consists of five interns, three assistant residents, and one resident. The interns first serve in obstetrics and then in gynecology, the gynecologic interns replacing them in obstetrics. Two of the interns are usually chosen to remain as assistant residents, and one of them finally elevated to the residency. During his five years of training, the obstetric resident has: a six months' internship in obstetrics and the same period of internship in gynecology; a one-year assistant residency in obstetrics at Hopkins and usually one year at the Boston Lying-In Hospital, part of the period as a member of Dr. Irving's house staff, and part with Dr. Hertig in his obstetric pathology laboratory. During his fourth year the man serves as

first assistant resident in gynecology at Hopkins, and during his fifth year he is the obstetric resident.

The senior staff is composed of full- and part-time members. The full-time members have sole supervision over the ward service and do the large bulk of the teaching. The part-time members conduct special clinics, and carry out a portion of the teaching. The private beds are shared by the full-time and part-time staffs, almost all of whom are previous Hopkins residents, actively engaged in teaching at their Alma Mater.

The postwar plans for the Department are still uncertain; however, it is hoped that it may rebuild and enlarge its physical plant. The full-time staff has been depleted by the war, but as soon as possible it will be restored to its normal complement.

ALAN F. GUTTMACHER.

Correspondence

Pitocin Versus Ergot

To the Editor:

May I draw your attention to a recent article in THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY by Dr. Leff, of New York? (June, 1945.) He has observed that there is distinct difference in the action upon uterine muscle of pituitrin and ergot preparations. Briefly, he states that pituitrin, acting physiologically, causes both contraction and retraction of the muscle fibers, leaving the organ in its ideal state following such injection. He points out that, on the other hand, the administration of ergot is followed by powerful uterine contraction but that retraction of the muscle is often absent, and feels that, when this is true, the contracted muscle is prevented from retracting. He feels that the use of ergot, before such permanent shortening has occurred, is unphysiologic and may be followed within an hour or two by hemorrhage. He recommends that pituitrin be given following the placenta, and ergot withheld until retraction has occurred, controlling any bleeding in the meantime by bimanual compression.

I wish to describe another method of giving the oxytocic drugs, which apparently does not conflict with this view. I refer to the intravenous injection of pitocin. In small doses, one or two units, this drug has been used in emergencies intravenously for many years with no ill effects. I first began using it routinely in 1940, after communications with the manufacturers had convinced me that it was safe in such a dose, well diluted. A 10 per cent solution is used, injecting 1 c.c. of the diluted drug. It can be injected directly by the use of a tuberculin syringe, being diluted by the repeated withdrawal of blood during the injection, but it is more convenient to prepare 10 c.c. in a sterile rubber stoppered bottle, using 1 c.c. of pitocin and diluting up to 10 c.c. with saline. One c.c. of this mixture can then be used.

Upon injection there is a dramatic contraction and retraction, usually within 20 to 30 seconds. This is followed by further rhythmic contractions and further retraction. In no case has there occurred any late bleeding, as seen with ergot preparations.

During the past several months this preparation has been used with the delivery of the baby, as recommended for ergotrate, by Davis and his associates of Chicago. In every instance, immediate separation of the placenta has occurred, with easy expulsion of the placenta by simple expression, in an almost bloodless manner. No case of incarcerated placenta has been encountered.

It would seem that the use of 10 per cent pitocin, the dose suggested, is more physiologic than ergot for the following reasons:

1. It promotes retractions of uterine muscle and is followed by normal rhythmic contractions, and is therefore merely an accentuation of the normal physiology.
2. If incarceration did occur, correction should be easy, because of its short action, as compared with longer acting ergot preparations.

If the use of 10 per cent pitocin intravenously becomes an accepted procedure, the manufacturers of the drug will doubtless feel impelled to prepare such solutions, in sterile 1 c.c. ampules, ready for instant use. Then we should have an efficient, cheap preparation at our disposal.

J. L. MACARTHUR, M.D.

DRUMMOND MEDICAL BUILDING,
MONTREAL, QUEBEC.
JANUARY 18, 1946.

Spontaneous Changes in Fetal Presentation

To the Editor:

In a recent reply to the question as to the fetus' changing presentation during pregnancy, authorities state that it is not unusual, but seldom has occurred more than twice. (J. A. M. A., Dec. 9, 1939, "Queries and Minor Notes.")



Fig. 1.—Breech Presentation, Jan. 9, 1945.



Fig. 2.—Vertex Presentation, Jan. 23, 1945.



Fig. 3.—Breech Presentation, Jan. 30, 1945.



Fig. 4.—Vertex Presentation, Feb. 2, 1945.

The following case is presented because of possible interest: The patient was a para II, aged 37 years, white, with a history of previous section, with uneventful recovery, in 1940, for cervical dystocia after a thirty hour labor. Her last period was April 13, 1944, and the patient

had some flowing on May 25, 1944. The approximate date was estimated to be Jan. 20, 1945. During the course of the pregnancy, x-rays were obtained to show that the fetus had changed presentation four times without manipulation, on the dates which are marked on the photographs. A low cervical cesarean section under spinal anesthesia with Madlener sterilization was carried out on Feb. 14, 1945. This date was selected rather than Jan. 20, because the baby did not seem quite large enough on abdominal palpation. An 8-pound boy with head in left occiput transverse position was extracted with forceps after rotating the face forward. The patient made an uneventful recovery.

HARRY M. KIRSCHBAUM, LT. COL., M.C.

CHIEF OBS. AND GYN. SERVICE,
PATTERSON FIELD HOSPITAL, FAIRFIELD, OHIO.
Sept. 20, 1945.

Vitamin E in the Menopause

To the Editor:

I have just seen the article by Dr. Christy in the July issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, which advocated the use of vitamin "E" for menopausal symptoms. There were some omissions in his bibliography, however, which I may be able to remedy.

The use of "E" for this syndrome was first suggested (1) in a paper read before the Toronto Academy of Medicine in 1937, reiterated at the vitamin "E" Symposium (2) in England in 1939, commented on by Anna Hain (3) in 1944, and again by the writer (4) in a letter to the *British Medical Journal* in that year. It does not seem to be the answer in every case, but it does help the majority of such patients, and is at least as valuable as the estrogens. There has been insufficient attention paid to the women either not helped or made worse by the use of the latter. Vitamin "E" has its role there. It is a great mistake to regard the estrogens either as the sole therapeutic agents in the management of the menopause or as being therapeutic agents only. They can do harm as well.

Dr. Christy quotes Mattill on the lack of data, suggesting that "E" has any relationship to the endocrine system. The evidence that it is anti-estrogenic in nature is considerable, however, and we are gradually accumulating further evidence pointing in the same direction. As early as eight years ago the writer observed, for example, that women having prolonged bleeding and clotting times usually had high blood estrogen levels, and that administering vitamin "E" rapidly restored these to normal. In 1941, both Castrodale and associates and Tyslowitz and his co-workers published reports to indicate that the administration of estrogens to dogs decreased blood platelets until even purpuric levels were attained. The latter observed prolonged bleeding times.

With regard to "Habitual Abortion," on which you have published two papers lately, by Dr. Quigley and Ingram, I believe that the principal value of vitamin "E" has is in the preconceptual treatment of the sire.

As vitamin "E" is so similar in action to progesterone, with the great additional advantage of being much cheaper and usable orally, it has a place in treating dysmenorrhea and the premature termination of pregnancy which it is too seldom accorded. Its effect upon many severe cases of vulvovaginitis, even upon some early leucoplakias, is remarkable, as is its influence on defective semen. There are reasons to think that it acts directly on kidney tubules, and thus its value in many late pregnancy toxemias may be explained.

If prophecies weren't quite out of date, it could be predicted that vitamin "E" would prove to be as widely useful as the estrogens, its antagonists. One wonders, for example, what its role may prove to be in the prophylaxis and control of fibroids and mammary cancer, if either of these are in any sense estrogenic in origin.

Perhaps I may in closing insist again that what Vitamin "E" can do will never be realized by most practitioners until a reliably stable and potent product is generally used.

E. V. SHUTE, M.D.

287 QUEEN'S AVENUE, LONDON, ONTARIO.
JANUARY 14, 1946.

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Comment by Dr. Christy

To the Editor:

I read with interest Dr. Shute's letter. The additional bibliography referring to my article is very informative but was not known to me, and the omission in my references was not intentional.

My reasons and purpose in undertaking this experimental study were stated in my article, and I had no previous knowledge or suggestions as to the physiologic role Vitamin E might play in menopause.

As this study progresses I am more and more convinced that while its role in human metabolism remains somewhat obscure, Vitamin E has demonstrated its effectiveness in menopausal therapy, and its chief advantage over estrogens is in the fact that it is well tolerated and is free of any stimulative effect on the genital system, even after excessive doses are given.

CHRIST J. CHRISTY, M.D.

663 N. OAK STREET, BUFFALO, N. Y.
JANUARY 24, 1946.

Department of Reviews and Abstracts

Selected Abstracts

Labor

Saltau, W. D.: The Indications for Surgical Induction of Labour, M. J. Australia 2: 424, 1944.

The author enumerates a list of conditions in which surgical induction of labor was indicated. Over 80 per cent of these cases were for toxemia of pregnancy. The two methods used were the rectal tube and artificial rupture of membranes. The latter method is the one that is favored. The risk of infection is higher with the rectal tube. Each patient, it is pointed out, is an individual case and has to be judged accordingly. Some of the conditions for which surgical induction of labor is indicated are mentioned.

WILLIAM BERMAN.

Hayes, W. Ivon: Medicinal Induction of Labor and Induction in Post-Maturity, M. J. Australia 2: 421, 1944.

The author feels that there are only four indications for the induction of labor by medical means:

1. In hypertension, renal toxemia, chronic nephritis, pyelitis and pyelonephritis, medicinal induction may be used once, if the head is low and the cervix partly obliterated; otherwise, a surgical induction should be used.

2. If premature rupture of the membranes has occurred, medicinal induction may be used once, or repeated but not if disproportion is present.

3. If the fetus is dead, medicinal induction may be used with stilbestrol.

4. Medicinal induction may be used as an adjuvant to surgical induction, which may be performed during the medicinal treatment or later if the surgical induction appears ineffective.

The author condemns the induction of labor for postmaturity. It is felt that induction of labor based on dates alone causes a more difficult labor and a higher fetal mortality rate than if patients are allowed to enter labor spontaneously. Induction therefore increases rather than diminishes the danger associated with it.

WILLIAM BERMAN.

Pregnancy, Diagnosis, Physiology, etc.

Hunt, A. B.: The Rh Factor in Repeated Abortion and Miscarriage, Proc. Staff Meet., Mayo Clin. 20: 26, 1945.

Over a two-and-one-half-year period, Hunt collected a small series of 25 cases giving a primary or secondary history of habitual abortion. The Rh factors were determined in this series. In but three instances were the patients Rh negative.

Eighty-eight per cent of these 25 patients were Rh positive and 12 per cent Rh negative. Among the 96 pregnancies only 9 (9.4 per cent) occurred among the Rh-negative patients. From this small series of cases, giving past histories of habitual abortion (and

Rh tested), the author concludes that the Rh factor, at least in a suggestive small series, is not of great importance as a common cause of repeated abortions and miscarriages. Hunt states the endocrine deficiencies of function of the pituitary, ovary, thyroid, and testes are probably of more importance in habitual abortion than is the Rh factor. There is no indication that the author suspected isoimmunization by the blood factors A and B as one of the several causes of early fetal death.

CLAIR E. FOLSOME.

Livio Martini, Juan: Changes in the Cervical Mucosa During Pregnancy, *Bol. Soc. de obst. y ginec.* 23: 157, 1944.

The author made a histologic study in 23 cases and found important changes in the epithelium, glands, and stroma of the cervical mucosa.

The epithelium shows proliferation sometimes assuming the aspect of stratified pavement epithelium. The glandular system presents hyperplasia and hyperfunction. The stroma shows increased looseness, edema, plasmacellular infiltration, new vascular formation, congestion, cavernous aspect, hemorrhagic infiltration, and histoid mobilization.

The endocervical mucosa is not expelled during labor, as claimed by Stieve whose assertion that the mucous plug consists of the entire endocervical mucosa is incorrect. The changes in the covering and glandular epithelium may simulate neoplastic lesions and lead to grave diagnostic errors.

Knowledge of the pregnancy changes of the endocervix and their study may mean a step toward the solution of the obscure etiological problem of cervical cancer, the incidence of which is now positively known to be in direct relation to the number of pregnancies.

J. P. GREENHILL.

Pregnancy, Complications, etc.

Mascaro Porcar, José M.: Varices and Pregnancy. Physiopathogenic Considerations for the Prophylaxis of Aseptic Embolism, *Toko-ginec. pract.* 3: 263, 1944.

The author states that action against the warning triad of possible thrombosis is always necessary at the time of labor.

Circulatory sluggishness is overcome by early mobilization (immediately after labor) of the lower extremities by the method of "walking in bed." A bottle is placed under the soles of the feet of the puerperal woman who then makes it rotate without losing contact with it.

To combat the increase in coagulability of the blood a 50 per cent heparin solution is given intravenously four times a day immediately after delivery, the doses being 50, 50, 50, and 100 mg. of the drug.

No action can be taken against the lesion in the vein, surgical treatment being inadvisable in pregnant women because the degree of the lesion which will persist after delivery cannot be foreseen. Prophylaxis of toxic factors may prevent endothelial disturbances, but the principal indication after delivery is to exclude from the circulation the veins whose walls may be altered. This is done with a bandage of elastoplast or adhesive zinc oxide plaster over the varicose areas.

J. P. GREENHILL.

Seaberg, S. P.: Report of Case of Osteomyelitis of Sacrum Complicated by Pregnancy, *West. J. Surg.* 52: 517, 1944.

A patient, aged 18 years, was seen on March 6, 1944, approximately four months pregnant, complaining of pain over the coccyx and sacrum. She was followed through a normal pregnancy with occasional complaint of pain in this area. She went into spontaneous labor, and upon examination at this time, a hard, apparently bonelike obstruction to the pelvic outlet was found. Cesarean section was done, and seven days later an x-ray of the lower spine

was done. A clinical diagnosis of osteosarcoma was made, and this was confirmed by the x-ray. The patient ran a low-grade temperature which did not respond to penicillin. Four weeks after delivery, fluctuating area over the sacrum appeared, which was incised and a penrose drain was left in the wound. Five days later the wound was reopened to obtain a biopsy, and a large cavity in the sacrum was found and irrigated. Pathologic diagnosis on the tissue removed was osteomyelitis. The offending organism was *Staphylococcus*.

WILLIAM BICKERS.

Bump, W. S.: Management of Toxemia in the Last Trimester of Pregnancy, Wisconsin M. J. 42: 1037, 1943.

The management of toxemia in the last trimester should begin as early as possible in pregnancy with measures designed to prevent an excessive gain in weight as well as the retention of water and sodium. The diet should contain an adequate quantity of protein but should be low in fat and salt. Under correct management severe pre-eclampsia seldom develops, and if adequately treated rarely results in eclampsia. When eclampsia does develop, treatment should aim at emptying the uterus by the safest means, but only after proper medical care. The essential principles involved in the treatment of eclampsia are the production of diuresis and the control of convulsions by proper sedation. The author follows very closely the management of toxemias as elaborated by Dieckmann in his book.

FRANK SPIELMAN.

Anatomy, Anomalies, etc.

Dunn, H. G., and Salter, J. G.: Recurrent Anencephaly, J. Obst. & Gynaec. Brit. Emp. 51: 529, 1944.

The authors report a case of recurrent anencephaly in fetuses born in two successive pregnancies in a woman 29 years of age. The rarity of recurrence of anencephaly is pointed out. This particular case occurred in a family that gave a familial history of spina bifida. The various etiological factors such as heredity, familial incidence, sex, maternal age, and birth order are discussed. The author concludes that the recurrence of malformations in siblings, sex, and racial incidence is strongly suggestive of a hereditary causation, but only family incidence is real proof. Unfortunately, the evidence for this is scanty in anencephaly. There is possibly an hereditary association between anencephaly and other congenital malformations, particularly of the nervous system.

WILLIAM BERMAN.

Snyder, Laurence H., and Doan, Charles A.: Studies in Human Inheritance, XXV. Is the Homozygous Form of Multiple Telangiectasia Lethal?, J. Lab. & Clin. Med. 29: 1211, 1944.

The authors present the clinical history and autopsy record of what is probably the first recorded instance of the homozygous form of multiple telangiectasia. The family history would seem to indicate that there is a semidominant lethal gene associated with this condition. Fortunately, all of the grandparents of this infant were available, and one maternal and one paternal grandparent revealed multiple telangiectatic areas of the skin. Both parents were also afflicted with this condition. The infant had a port wine birthmark over the left breast at birth. There was a progressive development of hemangiomas of the skin and mucous membranes, and by the twenty-eighth day hemorrhagic manifestations of the disease were present. The course was progressively downhill, and death occurred at 2 months and 18 days of age. Autopsy revealed multiple hemangiomas of the skin, mucous membranes, lungs, liver, spleen, kidneys, intestine, and brain.

LT. L. M. HELLMAN, MC, USNR

Warkany, Joseph: Congenital Malformations Induced by Maternal Nutritional Deficiency, *J. Pediat.* 25: 476, 1944.

Genetic, infectious, and actinic factors have been proved to be etiological principles leading to malformations in mammals, including man. It has been suspected that malnutrition of the embryo can also be considered an etiological factor; but there is little evidence that maternal malnutrition can interfere with the prenatal development of the fetus.

The authors, using rats for their experimentation, fed them on a diet deficient in vitamin A. The few rats able to terminate pregnancy produced young who were born blind, and had deformed eyes. Hale, in 1933, described anophthalmos, cleft palate, accessory ears, and misplaced kidneys in pigs born of mothers fed on a vitamin A deficient diet.

Another type of congenital malformation was induced by Warkany, Nelson, and Schraffenberger in about one-third of female rats that were raised and bred on a rachitogenic Steenbock and Black diet which was supplemented by vitamin D to prevent rickets. The abnormal young showed chiefly skeletal changes, such as shortness of the mandible, radius, ulna, tibia, and fibula, and cleft palate. These deformities, though occurring in various degrees and in different combinations, conform to a definite pattern.

These experiments prove that maternal dietary deficiencies in the rat can induce congenital malformations in the offspring. It remains to be seen if this holds true for congenital defects in man.

JAMES P. MARR.

Cancer, Malignancies

Peralto Ramos, A., Peralto Ramos, A. G., and Fortunato Albertelli, J.: Cancer of the Cervical Stump, *Obst. y ginec. latino-am.* 2: 517, 1944.

The authors observed four cases of cancer of the cervical stump at intervals varying from 2½ to 33 years since the time of operation. In spite of this, they believe that total hysterectomy is a much more formidable operation than the supravaginal one, hence they are not in favor of total hysterectomy as a routine procedure. The chief prophylactic against cancer of the cervical stump in the opinion of the authors is the colposcope.

The prognosis in cases of cancer of the cervical stump is bad. The authors prefer combined radium and x-ray treatments rather than operation.

J. P. GREENHILL.

Saphir, Otto, and Lackner, Julius E.: Adenocarcinoma With Clear Cells (Hypernephroid) of the Ovary, *Surg., Gynec. & Obst.* 79: 539, 1944.

Two yellow tumors of the ovary occurring in women of 46 years and 60 years, respectively, are described. These tumors were histologically malignant, and were made up of circumscribed areas of clear cells. They did not have any masculinizing effect, and were thus differentiated from luteinized granulosa-cell tumors. Similar new growths have been called hypernephroma of the ovary. It is also possible that some of these tumors have been included in the mesonephroma group. It is the opinion of the authors that, because of the resemblance between these tumors of the ovary and those occurring in the kidney, they should be designated as adenocarcinoma with clear cells or hypernephroid carcinoma. The lack of glomerular or tubule-like structure serves to differentiate them from mesonephroma.

LT. L. M. HELLMAN, MC, USNR

Johnson, J. R., and Dockerty, M. B.: Bilateral Brenner Tumors of the Ovaries: Report of a Case, *Proceedings of the Staff Meetings of the Mayo Clinic* 20: 120, 1945.

The authors present briefly the clinical and pathologic features of the Brenner type of ovarian tumor. Brenner tumors constitute about 2 per cent of all solid tumors of the ovary. All of the twenty cases, except the case herein reported, encountered at the Mayo

Clinic (1905 to 1942) were unilateral. This case of bilateral Brenner tumor is the fourteenth one to be reported, which denotes its extreme rarity clinically. There are no signs and symptoms which are pathognomonic of a Brenner tumor; microscopically, the chief danger is in mistaking Brenner tumor for epithelioma, primary or metastatic.

HARVEY B. MATTHEWS.

Gynecologic Operations

Da Costa, C. C.: Hysterectomy, With Conservation of Menstruation, *Obst. y ginec. latino-am.* 2: 589, 1944.

The author maintains that removal of the uterus does not result in degeneration of the ovaries in laboratory animals. Women who have had their uterus removed frequently continue to have ovarian function, as demonstrated by the persistence of menstrual crises, the finding of estrogen in the circulation, and the occurrence of pregnancy in the stump of an extirpated uterus. Therefore, whenever the author removes the uterus, he transplants two pieces of endometrium in the cervical canal. In his series of 19 cases, 14 women menstruated after operation and 5 did not. Of the 14 women who menstruated, 13 had no symptoms of the menopause, but among the 5 women who had amenorrhea, 4 had menopausal disturbances.

J. P. GREENHILL.

Peralta Ramos, A. G., and Gramajo, G.: Immediate and Late Results of the Wertheim-Schauta Operation, *Obst. y ginec. latino-am.* 2: 766, 1944.

The authors are opposed to the correction of prolapse of the uterus and retroflexion of the uterus by means of abdominal operations. They favor a modified Wertheim-Schauta interposition operation for such cases. In a series of 28 cases, 14 were followed up. Three women were found to have a return of the prolapse. The chief indication for the Wertheim-Schauta operation is a second degree prolapse with large cystocele and urinary incontinence. The risks of the operation are slight, and it can readily be performed entirely under local anesthesia.

J. P. GREENHILL.

Roberts, Maiben: An Analysis of 90 Cases of Transplantation of the Ureters for Obstetric Vesicovaginal Fistula, *J. Obstet. & Gynaec. Brit. Emp.* 51: 519, 1944.

The author reports a series of 90 cases of obstetric vesicovaginal fistula treated by ureterocolic anastomosis with an operative mortality of 14.4 per cent. The technique of the transplantation is discussed. The author prefers the transplantation of one ureter at a time by the simplest possible method. Special postoperative precautions and complications are mentioned.

WILLIAM BERMAN.

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BLOOD DISORDERS ASSOCIATED WITH PREGNANCY*†

The Value of Sternal Marrow Biopsy

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THE science of hematology has made distinct and rapid progress since the advent of sternal marrow biopsy. The hematologist has been able to study the blood cells in their formative stage. This knowledge has given him a new perspective into the diagnosis and management of the blood dyscrasias.

Pianese¹ (1903) was the first to obtain human bone marrow during life for examination. He punctured the femur of a patient, and obtained bone marrow for study. In this same year, Wolff² utilized trepanation of the tibia and femur in experimental animals, and he suggested the clinical use of bone marrow biopsies.

The pioneer of bone marrow biopsy was Ghedini.³ In 1908, he described a method of trephining the upper end of the tibia and making sections and smears of the curetted marrow from patients with latent malaria and leishmaniasis. He observed that parasites could be demonstrated in the bone marrow when absent in the peripheral blood; observations that have been repeatedly confirmed in recent years.

Seyfarth,⁴ in 1923, advocated the use of the sternum. He used a surgical technique, and removed a small piece of bone marrow. His method, somewhat refined, is still advocated by many hematologists.

Arinkin,⁵ in 1927, reported a simple painless method by which a small amount of bone marrow fluid was aspirated from the sternum for diagnostic purposes. This introduction of the needle puncture method was the greatest contribution to the simplification of the technique. He punctured the outer lamina of the sternum with a stout spinal needle with a tightly fitting trocar, and aspirated a mixture of blood and bone marrow. He made films of the aspirated material, and studied the stained slides histologically.

*Presented before the Chicago Gynecological Society, Jan. 19, 1945.

†These studies were made possible in part by a grant from Armour and Co., Chicago.

Since then, many experimental and clinical studies of the bone marrow have been made. The findings in both health and disease are well known. Bone marrow biopsy is now a standardized procedure in the study of the blood and its disorders. It is not a "cure all," but is important in the proper evaluation of abnormal blood states. In many cases it is the key to the diagnosis. The study of an abnormal blood picture is not complete without an analysis of the sternal marrow.

Although there are voluminous reports on the findings of the sternal marrow in health and disease, there have been extremely few studies in relation to the blood problems associated with pregnancy.

The myeloid, erythroid, and megakaryocytic groups of cells all originate within the bone marrow. This hemopoietic activity is constantly occurring, throughout life, in the marrow of the ribs, vertebrae, and sternum. The bone marrow of the long bones is relatively inactive, but remains as a reservoir that can become active when necessary. This hemopoietic activity of the sternal marrow is present at birth and sustained throughout life. The sternal marrow has been shown to be indicative of the character of the hemopoietic tissues as a whole.⁶

The two methods of sternal bone marrow biopsy in general use are the trephine and aspiration.

The trephine method is a surgical procedure. Under local anesthesia, a small incision is made into the sternum. A small piece of bone marrow is removed. Paraffin sections are made and stained for examination. Smears or imprints may also be made. While the topographic relationships of the marrow are preserved in sections, smear or imprints are necessary for accurate identification of the various cells seen in normal and pathologic conditions.

Although this biopsy method is preferred by many investigators, its great drawback is that it is a surgical procedure. Despite the anesthetic, it is often painful and cannot readily be repeated on the same patient. Turkel and Bethell⁷ have devised a special needle by which a small piece of marrow can be readily curetted and removed through a small puncture wound. This eliminates the "incision hazard" of previous techniques. However, one cannot study the marrow grossly with this method. Another objection is that frequently the tissue removed is too small to be of value.

Sternal aspiration has become the more popular method. The technique is simple, relatively painless, and can be repeated at will on the same patient. The one objection to this method is that along with aspiration of the bone marrow cells, one must of necessity withdraw sinusoidal (or peripheral) blood at the same time. This may dilute the bone marrow so greatly that one can only see a few bone marrow cells on a smear. This one objection has been overcome by the use of the concentration method of Limarzi.⁸

Technique

Limarzi Method.—The second or third interspace is selected for aspiration. Iodine and alcohol are applied to the skin. A small wheal containing 1 per cent procaine is made in the skin over the sternum with a fine hypodermic needle. About two to three cubic

centimeters are injected into the subcutaneous tissue and under the periosteum of the sternum. After anesthesia is obtained, the specially devised sternal needle* is gently but firmly inserted through the anterior wall of the sternum into the bone marrow. A definite "give" is felt as the needle enters the marrow. One cubic centimeter of bone marrow fluid is then aspirated into a dry syringe. This fluid, composed of sinusoidal blood, hemopoietic marrow, and fat, is immediately transferred to a small dry tube containing a minute amount of powdered heparin† as an anticoagulant. A Wintrobe hematocrit is then filled with the mixture and centrifuged at 2,000 R.P.M. for five minutes. This separates the hemopoietic marrow from the sinusoidal blood and fat. The fat and most of the plasma layer are then pipetted off and discarded. The hemopoietic layer plus a small unit of plasma is pipetted off, placed in a small watch glass, and mixed. Smears are then made in the usual manner, air-dried, and stained with either Wright's stain or with the May-Grünwald-Giemsa combination. When Wright's stain is used, allow the stain to act for three minutes; then dilute with as much distilled water as the slide will hold, mixing very thoroughly. Allow this to stand fifteen to twenty minutes, then wash with distilled water and air-dry. Cell counts also may be made from the mixture.

This method gives a gross approximately quantitative value as well as a constant qualitative bone marrow pattern. Limarzi has followed this method in some 2,675 sternal biopsies. The normal bone marrow pattern has been well defined and the variations from normal, as seen in the various hematologic disturbances, are well noted. Any individual possessing a normal amount of surgical skill can perform the sternal aspiration. Any experienced hematologist can recognize the morphologic appearances of the cells that may be encountered.

Clinically, all the blood disorders that may be associated with pregnancy can be classified in four general groups.

1. Anemia.
2. Conditions associated with enlargement of the lymph nodes, and splenomegaly.
3. Hemorrhagic disorders.
4. Ulcerative lesions of the oral cavity and other mucous membranes, in most instances due to granulocytopenia.

1. Anemia

Anemia is not a diagnosis. It is a symptom. Anemia indicates a decrease in the number of circulating erythrocytes, or reduction in the amount of hemoglobin below the normal standard for the age and sex of the individual. This is purely a peripheral blood evaluation, since anatomically the erythroid tissue may be hypoplastic, normal, or hyperplastic. This paradox is rather common in diseases of the hemopoietic organs.

The anemic state is the result of either (1) a loss of blood from hemorrhage, (2) increased blood destruction, or (3) decreased blood formation.

In recent years, the classification of anemia, based on the size and the hemoglobin content of the average erythrocyte, has proved more satisfactory from the standpoint of treatment than the complicated classifications used in the past. From the hemoglobin, erythrocyte, and hematocrit determinations, an anemia is classified as macrocytic, normocytic, simple microcytic, or hypochromic microcytic in type. (See Table I.)

*University of Illinois sternal needle. Made by V. Mueller & Co., 408 S. Honore St., Chicago, Illinois.

†Powdered Heparin, Lot Number 153. Hynson, Westcott, and Dunning, Baltimore, Maryland.

TABLE I. DETERMINATION OF THE TYPE OF ANEMIA

TYPE OF ANEMIA	MEAN CORPUSCULAR VOLUME (CUBIC MICRONS)	MEAN CORPUSCULAR HEMOGLOBIN (MICRO-MICROGRAMS)	MEAN CORPUSCULAR HEMOGLOBIN CONC. (PER CENT)	CELL DIAMETER (MICRONS)
Macrocytic	94 and over	More than 27	32 to 36	8.0 to 10.0
Normocytic	80 to 94	27 to 31	32 to 36	*7.5
Simple microcytic	80 and lower	Less than 27	30 or higher	6.0 to 7.0
Hypochromic microcytic	80 and lower	Less than 27	29 or less	6.0 to 7.0

*In familiar hemolytic icterus (spherocytic jaundice) 5.0 to 7.0 microns.

Anemia in Pregnancy

Normal Pregnancy (Physiologic Anemia).—Extensive studies have been made on the peripheral blood in pregnancy. The lowering of the hemoglobin level, erythrocyte count, and hematocrit reading commencing in the third or fourth month, progressing until the sixth or seventh month, and remaining low until delivery, with a return to normal in the puerperium, has been noted and confirmed by all investigators.⁹ However, there is no agreement as to the interpretation of these findings. Are these changes due to hydremia or a lack of iron and/or protein deficiency? All agree that a hydremia exists. Dieckmann¹⁰ states that these lowered values are normal during pregnancy and are due to the dilution of the blood by the tremendous increase in the plasma content. Adair and Dieckmann¹¹ say that only values below hemoglobin 10 grams and erythrocytes 3.36 million are abnormal. Bethell¹² says that hemoglobin 11.3 grams and erythrocytes 3.70 million are the minimum figures. Watson¹³ reports that the hemoglobin may fall to 7.7 grams merely from hydremia, while Whitby and Britton¹⁴ is of the opinion that an erythrocyte count below 4.0 million is pathologic. Various investigators have shown definite improvement in these blood values in cases treated with iron in comparison to control cases.¹⁵ Others¹⁶ have failed to note this improvement.

At its best, the peripheral blood is not always a true index of the hemopoietic state. The findings in the peripheral blood are too readily influenced by the physiologic reaction to food, muscular work, and emotional upsets. Likewise, hematologic technique is such that great error is possible in the performing of these seemingly simple tests. It has been shown that the error involved in the hemoglobin estimation via the Newcomber method is about 5 per cent. In normal patients the hemoglobin level may vary up to 15 per cent (2.07 grams) during the day. The erythrocytes may fluctuate within a 17 per cent range during the day, whereas, the potential error in the method of performing the count may vary from 2 to 13 per cent.¹⁷ With such frequent variations and possible errors present, one must be hesitant to state that a pregnant woman who already possesses a lowered hemoglobin level and erythrocyte count from the hydremia or increase in the plasma content is anemic. Likewise, all results from therapy must not be overrated.

The bone marrow, however, is stable. The findings in normal pregnancy are constant. We have previously reported¹⁸ our findings in a group of patients studied throughout pregnancy and others seen at various intervals of their pregnancy. In all cases, we noted a normal erythroid pattern. A slight

myeloid hyperplasia plus a tremendous increase in the megakaryocytes was present. In general, the bone marrow was hyperplastic throughout pregnancy, but qualitatively the erythroid development was normal. Correlative studies with the peripheral blood were made in all cases. We noted the same peripheral blood changes as found by other investigators.

The bone marrow rapidly reacts to changes in the peripheral blood. The loss of iron, be it due to its direct loss via bleeding, decreased absorption, or an increase in blood destruction, immediately stimulates the bone marrow to a greater effort. Earlier forms of erythroid cells predominate the marrow cells. This is called a normoblastic erythropoiesis and is a constant feature of such an anemic state.¹⁹ A normal bone marrow pattern is direct evidence of a normal blood picture. Anemia is never present when one sees such a bone marrow finding.

Therefore, we are definite in our opinion that the changes in the peripheral blood noted in normal pregnancy are merely due to the hydremia, and possess no relation to an anemic state. No treatment of any type is necessary. In suspect cases of anemia with peripheral blood levels below those given for normal pregnancy, the bone marrow pattern will determine whether one is dealing with an increase in the hydremia or the presence of a true anemia.

Iron Deficiency Anemia.—Many of these patients, exhibiting a lowering of the peripheral blood values below the minimum just mentioned, possessed bone marrows that showed a true normoblastic erythropoiesis in contrast to that as above described. Pronormoblasts and basophilic normoblasts were seen in large numbers. These cells represent a more immature type of erythroid development, and are the response of the bone marrow to the lack of iron independent of the cause. These patients promptly improved on adequate iron therapy and did not improve without treatment. With treatment, both the peripheral blood and bone marrow returned to the normal levels noted during pregnancy.

Thus, this normoblastic bone marrow readily denotes the presence of a true anemia and determines the type of treatment needed.

Megaloblastic Anemia (Pernicious Anemia of Pregnancy).—This anemia, although not common, is so severe, produces such a severe anemia, and responds so well to appropriate therapy, that its diagnosis must be considered in any severe anemic state associated with pregnancy. In patients with a severe anemia in which the cell size is definitely large (mean corpuscular volume over 100 cubic microns), the cell well filled with hemoglobin (mean corpuscular hemoglobin concentration, 32 per cent), and macropolycytes noted in the peripheral blood, the diagnosis is fairly obvious. However, as previously reported¹⁸ in three cases which we have seen, the peripheral blood findings varied in each case. Only one was typical of this anemia. The second was that of a normocytic anemia, and the third, that of a microcytic hypochromic anemia. Yet, in all cases, the sternal marrow analysis showed a typical megaloblastic marrow. Davidson²⁰ has reported similar observations. Adequate liver therapy and blood transfusions are lifesaving to these patients. Iron is futile except as an adjunct when the hemoglobin concentration is low.

The importance of an accurate diagnosis is readily apparent. We feel that one cannot truly diagnose this type of anemia from the peripheral blood alone. The findings are often confusing, whereas the sternal marrow aspiration is diagnostic.

Aplastic Anemia.—This severe anemia is essentially characterized hematologically by an anemia, leucopenia, and thrombocytopenia, and clinically by a marked waxy pallor, absence of enlargement of liver, spleen, or lymph nodes, and an acute fatal course. The bone marrow reveals a marked hypoplasia of all cellular elements. Occasionally, bleeding tendencies predominate the clinical picture, and thus lead to diagnostic error. This also occurs when ulcerative lesions of the oral cavity accompany the symptoms. Sternal marrow biopsy is diagnostic and will rule out the suspected purpura or agranulocytosis. Aplastic anemia may be primary (idiopathic) or secondary.

Secondary aplastic anemia is caused by chemicals and physical agents such as roentgen-ray and radioactive substances; and systemic diseases such as nephritis, metastatic carcinoma, sarcoma, Hodgkin's disease, and lymphatic leucemia, which either destroy or invade and replace the normal bone marrow elements. Sternal puncture is of aid in the diagnosis of such primary conditions.

Primary aplastic anemia, fortunately, is not common during pregnancy. Hurwitt and Field²¹ reported one such case and reviewed the literature in thirteen others. They are of the opinion that pregnancy may cause this hypoplasia of the bone marrow with its resultant peripheral blood findings. They report a case of Nieuwenhuis with such bone marrow findings. The pregnancy was terminated and recovery followed. The bone marrow revealed cellular elements four days after delivery. Of the fourteen cases studied, there were five survivals. In these, the patients all had the uterus emptied either spontaneously or by induction. Any patient who is pregnant and presents diagnostic evidence of an aplastic anemia with a hypoplastic bone marrow should have the pregnancy terminated at once. Repeated blood transfusions should be given until the bone marrow gives evidence of recovery.

However, until more cases are studied during pregnancy, one should make a poor prognosis, as most cases of primary aplastic anemia possessing a hypoplastic bone marrow run a rapidly fatal course, irrespective of treatment.

Occasionally, the bone marrow findings in cases of primary aplastic anemia reveal a hyperplastic bone marrow. This is the so-called pseudo-aplastic anemia. The course here is more chronic, and repeated blood transfusions may carry the patient along for some time. A pregnant individual may thus be carried until the fetus becomes viable. Frequent marrow analyses will aid in determining how long one may persist in an expectant attitude.

In secondary aplastic anemia, the prognosis depends upon the causative agent plus the bone marrow findings. The presence of a hypoplastic marrow is always grave. The causative disease in itself may be a fatal one. If so, one should treat the patient palliatively and allow the pregnancy to proceed, in the hope that a living child may be salvaged. Termination of the pregnancy will not alter the progress of the primary disease. Removal of the cause such

as chemical (arsenical, sulfonamides, etc.) or physical agents may be of aid. When such a cause is present, the conduct of the pregnancy will be determined by the bone marrow findings. Hypoplastic marrow—termination of the pregnancy; hyperplastic marrow—removal of the cause, repeated blood transfusions, and a conservative attitude toward the pregnancy.

Sternal marrow biopsy is thus an essential examination in all cases of suspected aplastic anemia. The findings are of great prognostic as well as diagnostic value.

Hemolytic Anemia.—Hemolytic anemia may be either intrinsic or extrinsic in character. The intrinsic anemias include *congenital* and *acquired hemolytic anemia*, *sickle-cell anemia*, and probably *Cooley's anemia* and erythroblastosis which, in many instances, has been shown to be associated with the Rh factor. A hemolytic anemia is sometimes seen associated with neoplasms, Hodgkin's disease, leucemia, and infections.

The bone marrow shows a normoblastic hyperplasia in these anemias. Sternal marrow biopsy is only of a "negative" value in that it rules out other types of blood disorders and encourages one toward further study of the disease; e.g., the search for the sickle-cell phenomena.

Congenital hemolytic anemia (spherocytic jaundice) is characterized by an anemia, a palpable spleen, an increase in the reticulocytes, and a lowered resistance of the erythrocytes to hemolysis in hypotonic salt solution. The red blood cells are spherical and small in diameter measuring five to seven microns (normal 7.5 microns). Pregnancy does not effect the course of the disease, since mothers have borne several children without any ill effects. Splenectomy results in a clinical cure.

Drugs, chemicals, certain parasites, and bacteria produce a hemolytic anemia. The hemolytic anemia that occurs during the administration of the sulfonamides produces a rapid and progressive drop in the hemoglobin and erythrocytes, a reticulocytosis, and a myeloid immaturity in the peripheral blood. The bone marrow shows a marked hyperplasia of the normoblastic tissue in all the hemolytic anemias secondary to increased blood destruction.

In general, the sternal marrow biopsy is not in a sense diagnostic in the hemolytic anemias but, in demonstrating the normoblastic erythroid response to the increased blood picture, does form a part of the diagnostic chain. Repeated blood transfusions and a conservative attitude toward the pregnancy are in order. Removal of the cause, as in the case of drugs, chemical, bacteria, and parasites, is of course, essential. Splenectomy following the delivery of the baby should be considered when indicated.

Elliptical red corpuscles, or ovalocytosis, is a hereditary trait transmitted by either sex, possibly as a simple Mendelian dominant. One case in a colored pregnant woman was accidentally observed. Except for the large number of elliptical red corpuscles, the blood studies were normal. The bone marrow was normal, and the ovalocytes seen in the marrow smear were probably due to dilution with peripheral blood. The anomaly of the red cells does not occur until after the nucleated red cells in the bone marrow extrude their nuclei.

Case Report

M. D., a 28-year-old gravidi ii, para i, was seen in the obstetric clinic on Aug. 15, 1938. Her last menses occurred on June 17, 1938. She appeared to be in good health, and pelvic examination revealed a six weeks intrauterine pregnancy. The past history was negative, except for the presence of symptoms of hyperthyroidism in 1932, which were relieved by a thyroidectomy in 1934. Her first pregnancy (in 1936) was uneventful. Labor was somewhat prolonged because of a generally contracted pelvis, and was terminated by a midforceps delivery. The child was normal and healthy. The congenital blood abnormality was not noted during the first pregnancy, but was found at the initial examination during the second. The essential blood findings were: hemoglobin, 10 Gm.; erythrocytes, 3,360,000; hematocrit, 29 per cent; icterus index, 10 units; platelets, 246,000; and reticulocytes, 2 per cent. The differential blood smear showed normal leucocyte findings. Seventy-four per cent of the erythrocytes were elliptocytes. The bone marrow was normal. A spontaneous abortion terminated the pregnancy on Sept. 8, 1938. The husband's blood was normal. The one child, aged 17 months, had 6 per cent ovalocytes in the blood smear. Siekling phenomena was not noted.

2. Enlargement of the Lymph Nodes and Splenectomy

Acute and chronic infections of the head and neck are the most common causes of localized lymphadenopathy. The peripheral blood usually shows a leucocytosis with a preponderance of young toxic granulocytes (shift to the left). Occasionally a leucopenia is present. The bone marrow shows a mild myeloid hyperplasia. Sternal marrow biopsy here would merely eliminate the possibility of a blood dyscrasia.

Infectious mononucleosis, or glandular fever, is not uncommon, and may occur during pregnancy. The presence of atypical lymphocytes (not monocytes) in large numbers in the peripheral blood are diagnostic but may lead to the suspicion of a leucemia. The bone marrow is hyperplastic with a moderate to marked granulopoietic immaturity. This is never carried to the stage of myeloblastic involvement. The heterophile antibody reaction is usually positive, but occasionally may be negative. When this occurs, sternal aspiration will rule out the suspicion of a leucemia.

Leucemia.—The leucemias may be divided into acute and chronic leucemia, and subleucemic types. Cases which live six months or less are said to be acute, the remainder are chronic. Subleucemia is used when the total leucocyte count is low or practically within normal limits. The leucemic state may be (1) myelogenous, a disorder of the bone marrow characterized by abnormalities of granulocytic formation; (2) lymphatic, a disorder of lymphatic formation; and (3) monocytic, characterized by the presence of normal and immature monocytes in the peripheral blood plus a hyperplasia of the reticulo-endothelial system. Only the myeloid and lymphatic types have been observed during pregnancy. Recent investigators have found 79 true cases reported in the literature.²²

The diagnosis of leucemia is usually obvious from the clinical symptoms and the peripheral blood findings. Sternal marrow biopsy is merely confirmatory. However, a not too uncommon type of leucemia is the subleucemic type. Here the blood merely shows a mild anemia and often a leucopenia. Abnormal (immature) forms may be few or absent. The sternal marrow will be filled

with highly immature leucocytes. Sternal aspiration here is diagnostic as the peripheral blood findings may be obscure. Alt²³ has reported just such a case.

The pregnancy should be followed conservatively in a leucemic patient in the interest of the child, since leucemic mothers give birth to normal children.²² All forms of leukemia are invariably fatal. An adequate diet, liver, iron in large doses, vitamins (especially the B complex), and rest in bed during the acute exacerbation are of help. Arsenic therapy in the form of Fowler's solution (liquor potassium arsenite), roentgen-ray therapy to the spleen or affected lymph nodes (except in the acute and leucopenic phase), and frequent blood transfusions are all of temporary value. Radioactive phosphorus has recently proved of value in the treatment of chronic myeloid leukemia, but it is not curative.

Chronic Myeloid Leucemia (Case Report)

Mrs. A. B., aged 21 years, entered the hematology clinic on April 20, 1938. She was referred to this clinic for treatment of chronic myelogenous leukemia. The diagnosis was confirmed by the hematologic investigation (see Table II). She was always in good health until the onset of the present illness. When she was sixteen years of age, she gave birth to her first child. The pregnancy and labor were normal. Two years later, she delivered a second child and again the pregnancy was uneventful. Shortly after this she complained of pain in the left lower costal region. An enlarged spleen was palpated and the blood dyscrasia diagnosed. Roentgen-ray therapy to the spleen was given at another hospital. Two years later she delivered her third child. She was exceedingly weak and noted ankle edema during this pregnancy. Labor was rapid and normal. Following her initial visit

TABLE II. CHRONIC MYELOGENOUS LEUCEMIA

	BEFORE PREGNANCY	PREGNANT AT TERM	4 DAYS POST PARTUM	6 MONTHS POST PARTUM
Hemoglobin (grams)	9.5	9.75	10.25	
Erythrocytes	3,500,000	3,800,000	3,410,000	
Leucocytes	250,000	105,000	60,000	250,000
Hematocrit (R %)	29	31	30	
Hematocrit (W %)	13.5	3.5	3.0	
Sedimentation (mm./hr.)				
Uncorrected	28	45	50	
Corrected	8	24	26	
Icterus index (units)	5	5	5	
Reticulocytes (%)	0.9	0.5	0.3	
Platelets	increased	normal	normal	
M.C.V. (c.u.)	89.2	81	88	
M.C.H. (m.m.)	29.2	26	30	
M.C.H.C. (%)	32.7	31	34	
Differential smear (%)				
Myeloblasts	0	1	0	
Eosinophilic myelocytes	1	0	0	
Promyelocytes	3	0	0	
Myelocytes	2	16	10	
Metamyelocytes	35	5	7	
Stab forms	0	12	7	
Polymorphonuclear neutrophils	51	55	67	
Lymphocytes	2	1	1	
Monocytes	0	2	2	
Eosinophils	2	4	3	
Basophils	4	4	3	
Bone marrow—Hyperplastic				
Predominant granulopoietic elements				

R = red cells. W = white cells. M.C.V. = mean corpuscular volume. M.C.H. = mean corpuscular hemoglobin. M.C.H.C. = mean corpuscular hemoglobin concentration.

to the hematologic clinic she received some roentgen-ray therapy (650 r. in four treatments) to the spleen. She next returned to the hospital on July 10, 1939, pregnant and near term. Except for the presence of the leucemia, her general health appeared good. An episode of mild vaginal bleeding occurred. When she was three weeks past term, medical induction was attempted, but this was unsuccessful. Labor was then induced by means of a Voorhees bag, and a normal delivery of a 2,980-gram healthy infant occurred six hours later. The puerperium was uneventful. Since then, she has received roentgen-ray therapy to the spleen on several occasions. When last seen her general health was fair and the leucemic state still chronic. All children are healthy, none showed any type of blood disorder.

Splenomegaly without lymphadenopathy has been reported many times during pregnancy.²⁴ Enlargement of the spleen is observed in most diseases of the hemopoietic organs, in circulatory disturbances, infections, metabolic disturbances, primary tumors, and in a number of unclassified conditions.

Banti's disease is a condition characterized by splenomegaly, anemia, leucopenia, and, in many cases, by a thrombocytopenia. When the condition has progressed to a later stage, cirrhosis, jaundice, and ascites complete the picture. Several theories have been suggested as the cause of the disease, an infectious process as the causative agent, and mechanical factors producing the symptom complex. In this group of conditions are included *idiopathic splenomegaly*, *splenic anemia*, and *thrombophlebitis of the splenic or portal veins* which are considered as phases of the same disease process.

The bone marrow in Banti's disease and closely allied conditions in the earliest stage shows a myeloid hyperplasia and there is an anemia and leucopenia in the peripheral blood. Later in the disease, the bone marrow shows a maturation arrest of the myeloid and megakaryocytic tissue with a leucopenia, neutropenia, thrombocytopenia, and myeloid immaturity in the peripheral blood.²⁵

Pregnancy under such conditions should be allowed to proceed in the usual manner. Following delivery of the child, splenectomy should be strongly considered, since the removal of the spleen, even in the later stage described, will restore the bone marrow and the peripheral blood to normal. On the other hand, in the last stages of the disease when cirrhosis of the liver is present, the bone marrow biopsy shows a marked erythroid immaturity as well as the above changes in the myeloid tissue. The presence of these findings speaks against splenectomy, as the results here are poor.

Banti's Disease (Case Report)

M. D., a 25-year-old gravida iii, para ii, was seen in the sixth month of her pregnancy on July 25, 1944. For the past month she complained of an aching pain in the left side of her upper abdomen. The spleen was found to extend four fingers breadth below the costal margin. This patient was referred in consultation by Dr. Robert E. Lee, who has continued to care for the patient. The blood findings are shown in the accompanying table. The pregnancy proceeded uneventfully followed by a normal spontaneous delivery on Oct. 12, 1944. The patient and the child are both in excellent health.

We have a second case under observation in which the spleen had been removed previously because of Banti's disease. During the pregnancy, the patient developed an anemia which has responded to iron therapy and repeated blood transfusions. She is being allowed to proceed with the pregnancy. Multiple vitamins, including vitamin K,

TABLE III. BANTI'S DISEASE

Hemoglobin (grams)	9.5
Erythrocytes	3,740,000
Leucocytes	5,000
Hematoerit (%)	37
Sedimentation (mm./hr.)	
Uncorrected	30
Corrected	20
Icterus index (units)	7.5
Reticulocytes (%)	3.2
M.C.V. (c.u.)	98
M.C.H. (m.m.)	26
M.C.H.C. (%)	27
Platelets	adequate
Differential smear (%)	
Stab forms	5
Polymorphonuclear neutrophils	71
Lymphocytes	20
Monoocytes	2
Eosinophils	2
Basophils	0
Bone marrow—Myeloid hyperplasia	
No malarial parasites in blood or bone marrow	

liver extract intramuscularly, and choline are being given to protect the liver. Liver function tests and blood protein determinations are being made at repeated intervals.

In most instances a generalized progressive enlargement of the lymphoid tissue speaks for malignant neoplastic disease. A practically normal white cell count in an individual with enlargements of the lymph nodes with or without a splenomegaly is suggestive of *Hodgkin's disease* or *lymphosarcoma*. These two conditions fall into the group of diseases called *lymphoblastoma* which include *lymphatic leucemia* and *mycosis fungoides*. Except for lymphatic leucemia, a biopsy of lymph nodes is required for a final diagnosis.

In *Hodgkin's disease*, the bone marrow is usually hyperplastic and of a myeloid or megakaryocytic type, depending upon the stage and severity of the process. An increase in the number of plasma cells, histocytes or reticulum cells, and eosinophiles are observed during some phase of the fatal condition. An anemia is present in the peripheral blood. Pregnancy is not affected by, nor does it affect, this chronic slowly progressive disease. The pregnancy may be treated in a conservative manner. Roentgen-ray therapy to the affected lymph nodes may prolong the course of the disease.

Hodgkin's Disease—Case Reports

CASE 1.—Mrs. L. K., a 20-year-old gravida i, para 0, entered the obstetric clinic on April 30, 1938, for prenatal care. Her last menses began on Feb. 16, 1938, and the expected date of delivery was Nov. 23, 1938. She was found to be about two and a half months pregnant. The past history was essentially negative, except for one visit to the clinic on Feb. 3, 1938, because of recurrent sore throats and swollen glands in the neck. At this visit in February, the ear, nose, and throat department did not find any pathology. On the first prenatal visit she appeared to be in good health and routine pregnancy care was advised. The blood findings are shown in the accompanying table. On June 21, 1938, when the patient was five months pregnant, a cervical adenitis was noted. Hematologic studies were performed, and the findings of anemia in the peripheral blood noted. The bone marrow showed a normal erythroid pattern, a myeloid hyperplasia, and an increase in the megakaryocytes. A biopsy of a cervical

TABLE IV. HODGKIN'S DISEASE. CASE 1

	3 MO. PREG.	5 MO. PREG.	1 YR. LATER	5 YR. LATER
Hemoglobin (grams)	70%	9.8	70%	60%
R.B.C.	3,850,000	3,200,000	4,010,000	3,450,000
W.B.C.	17,700	10,050	11,700	9,900
Hematocrit (%)		30		
Sedimentation (mm./hr.)				
Uncorrected		62		
Corrected		34		
Icterus index (units)		2.5		
Reticulocytes (%)		1.1		
Platelets		350,000		
M.C.V. (c.u.)		93		
M.C.H. (m.m.)		30		
M.C.H.C. (%)		30		
Differential smear (%)				
Metamyelocytes		1		
Stab forms		28		
Polymorphonuclear neutrophils		54		
Lymphocytes		12		
Monocytes		4		
Eosinophils		0		
Basophils		1		
Bone marrow—Myeloid hyperplasia				
Normal erythropoiesis				
Increase in megakaryocytes				

gland revealed the typical pathologic picture of Hodgkin's disease. Pregnancy was uneventful, and on Oct. 23, 1938 (36 weeks), a 2,550-gram girl was spontaneously delivered following a rapid, normal labor. This patient has been seen at frequent intervals since then and has run a chronic slowly progressive downhill course (See Table IV).

CASE 2.—A. A., a 32-year-old gravida i, para 0, was well until 1935 (aged 27 years) when she noticed a large nodule in her neck and in the axillary region. Biopsy of the cervical node showed the presence of Hodgkin's disease. She received small amounts of roentgen-ray treatments to these nodes in 1939. Pregnancy occurred in 1940. A 2,430-gram healthy infant was delivered spontaneously at term on Sept. 1, 1941, following an

TABLE V. HODGKIN'S DISEASE. CASE 2

	BEFORE PREG. 11/16/39	DURING PREG. 3/8/40	4 YR. LATER 12/19/44
Hemoglobin (grams)	9.75	10	8
Erythrocytes	4,210,000	4,750,000	3,600,000
Leucocytes	19,600	16,300	26,400
Hematocrit (%)	34	34	27
M.C.V. (c.u.)	81	71	75
M.C.H. (m.m.)	23	21	22
M.C.H.C. (%)	29	27	21
Icterus index (units)	2	5-7.5	0
Reticulocytes	0.3	0.5	0
Sedimentation (mm./hr.)			
Uncorrected	59	55	47
Corrected	36	38	19
Differential smear (%)			
Stab forms	8	30	12
Polymorphonuclear neutrophils	73	51	80
Lymphocytes	11	10	8
Monocytes	8	7	0
Eosinophils	0	2	0
Basophils	normal	normal	normal
Bone marrow—Myeloid hyperplasia			
Increased megakaryocytes			
Normoblastic erythropoiesis			

uneventful pregnancy and a normal labor. The course since then has been a chronic progressive downhill one. At the present time the patient is hospitalized because of anemia and a low grade febrile state (see Table V).

Lymphosarcoma spontaneously, or following roentgen-ray therapy may be converted into a condition called *leucosarcoma*. Here the bone marrow cells are invaded and replaced by the malignant cells. This is reflected in the peripheral blood by an anemia, granulopenia, and thrombocytopenia.

3. Hemorrhagic Disorders

Hemorrhagic diseases may occur during pregnancy. The tendency to bleed from mucous membranes and into the skin with the formation of petechiae and ecchymoses may be the symptom of an underlying disease or the bleeding manifestation itself may be the primary feature of the disease.

The mechanism in abnormal bleeding usually involves one or more of the following factors: (1) quantitative or qualitative changes of the platelets; (2) disturbances in the clotting mechanism; and (3) increased permeability of the capillary wall. In general, three tissues are primarily concerned in hemorrhagic disorders. They are the bone marrow megakaryocytes, which produce the blood platelets and in turn furnish the thromboplastin; the liver, which supplies the prothrombin, heparin, and fibrinogen; and the blood vessels, with their endothelial function and capillary reactions. The spleen is a disturbing factor in some thrombocytopenic states, and the gastrointestinal tract participates in the mechanism of vitamin K formation and absorption.

The term *thrombocytopenic purpura* is used to describe all cases presenting episodes of spontaneous bleeding from the mucous membranes and into the skin. This may be primary (without a known cause) and termed essential idiopathic thrombocytopenic purpura or it may be secondary.

In *primary idiopathic thrombocytopenic purpura* the bleeding time is prolonged. The coagulation time may be normal, but the clot retraction is poor. A differential smear or platelet count reveals the small number of blood platelets. These findings plus the clinical history makes the diagnosis obvious.

The bone marrow findings are essential as a guide to therapy. Where one finds an abundance of megakaryocytes in the bone marrow the prognosis is good. It is not known why this paradox of an absence of platelets in the peripheral blood and an increase of megakaryocytes in the marrow should occur. Some feel the spleen is disintegrating the platelets at too great a rate; but Limarzi²⁶ feels that the megakaryocytes are developing abnormally and thus cannot get out into the circulation. Patients with bone marrow findings, as described, respond rapidly to splenectomy. The peripheral blood and the bone marrow returns to normal and the bleeding tendencies disappear.

Many cases of essential thrombocytopenic purpura have been followed during pregnancy.²⁷ Splenectomy has been reported during pregnancy.²⁸ We feel that one should adopt a conservative attitude toward the pregnancy. Adequate diet, bed rest as needed, and repeated blood transfusions of fresh blood to keep up the peripheral blood levels should be administered during

the pregnancy. Splenectomy is best done following the pregnancy and during a remission of the disease, but may be performed if the patient is seen during the first trimester.

Purpura (Case Report)

B. P., an 18-year-old gravida i, para 0, entered the hospital because of a severe nose-bleed with evident loss of blood. Examination revealed evidence of the nasal bleeding plus blood colored gingival margins. The patient stated that following an appendectomy in 1938 she had often noted attacks of bleeding from the gums, nose, rectum, and into the skin. These attacks had of late been increasing in severity and intensity. On the date of admittance (June 20, 1940) she was found to be in the sixth month of her pregnancy. Her last menses began on Dec. 17, 1939, and her expected date of delivery was Sept. 20, 1940. Her pregnancy had been uneventful to the day preceding admission, when nasal bleeding occurred (except for an occasional spell of nausea and vomiting in the first trimester and slight bleeding from the gums). The hematologic findings are shown in the accompanying tables. Bed rest, nasal packing, and two 500 cubic centimeter transfusions

TABLE VI. PRIMARY THROMBOCYTOPENIC PURPURA

	6 MONTHS	8 MONTHS	20 DAYS POST PARTUM	AFTER SPLENECTOMY
Hemoglobin (grams)	9.8	10	14.5	17.5
Erythrocytes	3,120,000	3,250,000	4,810,000	5,910,000
Leucoocytes	17,150	9,200	9,950	9,550
Hematocrit (%)	26	32	44.5	58.5
Bleeding time (min.)	2.5	3	3	3
Coagulation time (min.)	9	15	15	15
Clot retraction (min.)	90	60	48 hr.	0
M.C.V. (c.u.)	83	98	92	98
M.C.H. (m.m.)	31	30	30	29
M.C.H.C. (%)	37	31	32	30
Reticuloocytes (%)	7	1	0.8	1.0
Icterus index (units)	5	5.75	5	7.5
Sedimentation (mm./hr.)				
Uncorrected	65	60	25	1
Corrected	29	40	28	19
Platelets	115,000	190,000	40,000	200,000
Differential smear (%)				
Myelocytes	4	0	0	0
Stab forms	20	10	6	6
Polymorphonuclear neutrophils	50	65	65	64
Lymphocytes	7	14	19	11
Monocytes	14	9	5	11
Eosinophils	5	2	3	5
Basophils	0	0	2	3
Bone marrow—				
Myeloid hyperplasia				
Normoblastic erythropoiesis				
Megakaryocytes increased				

of whole blood stopped the bleeding and improved the blood picture. Frequent small blood transfusions were given weekly until delivery. The pregnancy then proceeded uneventfully, and a normal female child was delivered spontaneously at term (Sept. 29, 1940) after a normal labor. The third stage was short and uneventful, the total blood loss being 150 cubic centimeters. Five hundred cubic centimeters of whole blood was given immediately after delivery. Puerperium was uneventful. Splenectomy was performed on Oct. 23, 1940. The spleen weighed 239 Gm., and the pathologist's report was "spleen consistent with thrombocytopenic purpura." Complete recovery followed.

Occasionally in essential thrombocytopenic purpura with clinical and peripheral blood findings as described, the bone marrow will show a hypoplasia of the megakaryocytes: Here one is dealing with a form of thrombocytopenic

purpura in which splenectomy will fail to be of any value. This type usually runs an acute rapidly fatal course. Perhaps the uterus should be emptied in this "malignant" form of thrombocytopenic purpura.

Secondary or symptomatic thrombocytopenic purpura may be due to other conditions. Numerous classifications of the purpuric states have been presented. The common characteristic of all purpuras other than the primary type is the presence of a causative factor.

Many purpuric states are merely symptoms of other blood dyscrasias such as aplastic anemia, leucemia, leucosarcoma, etc., as previously described. The predominant bleeding factor plus inconclusive evidence in the peripheral blood may lead to an incorrect diagnosis. Sternal aspiration will be the key to the diagnosis.

Bleeding tendencies are often noted as due to drug idiosyncrasies (such as belladonna, quinine, and sulfapyridine). Here clot retraction is normal, as is the bone marrow.

The sternal bone marrow findings in these hemorrhagic disorders tend to denote the presence or rule out the existence of a true blood dyscrasia, and in true primary idiopathic thrombocytopenic purpura offers a guide to treatment.

4. Ulcerative Lesions of the Numerous Membranes, Especially the Oral Cavity

Ulcerative lesions of the oral cavity and other mucous membranes are a common finding in a group of conditions called granulocytopenia or agranulocytosis. Granulocytopenia is classified as primary or secondary.

The primary type is characterized by a marked reduction in the white count (leucopenia) and a few and sometimes no granulocytes (neutropenia) on blood smear examination. The other blood elements are not affected. The patient feels extremely ill and looks toxic. The lymph nodes of the neck are frequently enlarged. Soreness of the throat, ulceration and necrosis of the mouth and pharynx occurs. These lesions may occur in the mucous membranes of any part of the body.

The pharynx appears diffusely purplish red, thus differing from the bright red and streaked throat of acute tonsillitis. This suggests breaking down of the tissue in the absence of polymorphonuclear neutrophils. The mortality in the acute cases in some series is as high as 90 per cent. Among the causes of granulocytopenia are drugs, fatigue, and infections. The drugs include amidopyrine (pyramidon), dinitrophenol, arsenicals, gold salts, sulfanilamide, and related compounds. Most of these agents are secondary causes of granulocytopenia. More often no cause can be found for the primary malignant neutropenia. The bone marrow shows aplasia or a hyperplasia with a maturation arrest of the myeloid series. The chance of recovery from the disease is best in patients showing a maturation arrest of the granulocytic tissue and a pronounced and sustained monocytosis in the peripheral blood. The therapeutic agents that are used in the treatment include stimulating doses of roentgen ray, adenine sulfate, pentnucleotide, liver extract, iron, yellow bone marrow concentrates, leucocytic extract, and small transfusions of fresh blood.

Inflammatory changes in the oral cavity, such as ulcerations and necrosis with membrane formation, and a leucopenia and neutropenia, can occur in acute poisoning, acute and chronic leucemia, aplastic anemia, sepsis, diphtheria, and infectious mononucleosis.

Besides pale and bleeding gums, the lesions in leucemic processes involving the mouth include swelling, hypertrophy and destruction of the interdental tissue following necrosis. These changes in the oral cavity may resemble those seen in patients with scurvy, acute stomatitis due to a variety of conditions, and Vincent's infection. Necrosis of the mucous membranes of the oral cavity is seen on the palate, cheeks, lips, and gums. Necrotic lesions of the tonsils and pharynx occur in acute leucemia.

Acute follicular tonsillitis, peritonsillar abscess, diphtheria, tuberculosis, syphilis, and fusospirochetal disease will not be confused with leucemia and other conditions that cause leucopenia, neutropenia and ulcerations of the oral cavity if the following factors and examinations are kept in mind: (1) careful inquiry concerning the use of drugs, (2) history of exposure to overdosage of roentgen rays or radioactive substances, (3) detailed blood and bone marrow studies and (4) laboratory aids such as blood cultures, bacteriologic studies of the oral lesions, sputum examinations, blood Wassermann reaction, and several of the tests previously mentioned.

Summary

In the past, the obstetrician's main interest in the blood findings associated with pregnancy has been in the clinical interpretation of the commonly noted lowered hemoglobin level and erythrocyte count seen in healthy individuals during pregnancy. In more recent years, the association of pregnancy and the various blood disorders has gained his attention, but unfortunately he has not made use of the sternal marrow findings. The hematologist, likewise, has not yet considered the problems of pregnancy in the light of the information obtained from bone marrow studies. It is only through cooperation of the hematologist and the obstetrician that such a relatively new procedure can reach its proper place in clinical investigation.

Bone marrow biopsy is not the sole method or answer to hematologic diagnosis. Although it is merely a part of the diagnostic "blood work-up" it is a most important one. The standard peripheral blood studies are still of major importance, and in many cases the sternal marrow findings may be only confirmatory. Yet, peripheral blood studies, especially in pregnancy because of the hydremia factor, often do not give one sufficient information, or may even give a false clue to diagnosis. Sternal marrow biopsy then becomes mandatory.

Sternal marrow aspiration (puncture method) using the concentration technique enables one to obtain a gross impression of the state of the bone marrow; and the well-developed "sternal hemogram" reveals more than enough marrow cells to enable the hematologist to readily discern the bone marrow pattern.

The normal erythroid marrow findings noted in healthy patients during pregnancy are conclusive in revealing that the lowered peripheral blood levels are due only to a hydremia, and speak for normal findings during pregnancy associated with blood dilution.

The characteristic marrow pattern noted in the various blood dyscrasias is of diagnostic, prognostic, and therapeutic importance in the management of both the hematologic and obstetric problems.

One of the greatest values of sternal marrow biopsy is its "negative value." The finding of a normal type of bone marrow definitely rules out the presence of a primary blood disease. The only exception is in cases of aleukemic lymphadenosis. (Lymph node biopsy will be needed.)

Conclusions

1. The cooperation of the hematologist and the obstetrician is essential to the proper management of blood disorders during pregnancy.

2. Sternal puncture with the concentration method of analysis is the preferred technique during pregnancy.

3. Sternal marrow analysis is an essential procedure in the diagnosis of the blood disorders associated with pregnancy.

4. Sternal marrow analysis is often the key to diagnosis and the guide to prognosis, and therapy both from the viewpoint of the hematologist and the obstetrician.

5. A group of illustrative blood disorders occurring during pregnancy are reported.

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Discussion

DR. HENRY L. SCHMITZ.—There has been considerable discussion concerning the relative value of the trephine method and the aspiration method of bone marrow biopsy. Limarzi's technique, which Dr. Wolff has employed, overcomes the objection of dilution in the aspiration method, but I think it should be pointed out that certain other objections can be raised. These objections are that the material withdrawn by aspiration may not be representative, that the cells do not retain their original relationships, and that the cells may not retain their relative proportions. Because of these factors, it is conceivable that one may get a false impression concerning hyperactivity, hypoplasia, or defective maturation of cells. In spite of these objections, we feel that the method is of unquestioned value if the results are used in conjunction with other clinical and laboratory findings. Most of the objections enumerated can be overcome if the aspiration is repeated whenever there is any question about the findings.

The value of bone marrow studies in interpreting the blood picture in health and disease is illustrated especially well, I think, by the findings in normal pregnancy. I have the feeling, although I have no actual figures to support this view, that true iron deficiency anemia is probably more frequent in pregnancy than Dr. Wolff's paper would lead us to believe. One gets this impression also from the reports of Gasul, Heath, Bethel, and others. If we consider the many possible etiologic factors, I think it is surprising that anemia does not occur more frequently. First, there is the increasing demand on the part of the fetus for iron and for red cell forming materials. Second, there are a number of factors that tend to limit the supply of these materials. Gastrointestinal disturbances which interfere with the ingestion of food are frequent. There are various toxic manifestations which may necessitate restriction of certain articles of food. Especially during the depression, there were many clinic patients who were on inadequate diets because of financial reasons. Finally, even when the intake of food is adequate, there may be deficient absorption or utilization of iron, as Strauss and Castle pointed out, due to hypo- or achlorhydria. All these factors disturb the normal balance that exists between the demand for and the supply of iron. I do not think we can draw a sharp line of demarcation between normal and abnormal blood findings in pregnancy. The values in nonpregnant women vary too much. A woman with a normal hemoglobin of 12.5 Gm. may have a reduction to 10 Gm. in pregnancy, which can be accounted for by hydremia. However, in a patient with a normal of 15 Gm., a reduction to 10 Gm. would make one think of a hypochromic anemia. I do not think it is desirable to do routine bone marrow punctures in pregnancy. It seems to me it is sound practice to administer small doses of iron to the pregnant woman in order to forestall the occurrence of an iron deficiency anemia. Another reason for administering pro-

phylactic doses of iron is the possibility that the infants born of anemic mothers are more likely to develop iron deficiency anemia during the first year of life, due to inadequate storage of iron in utero.

DR. HOWARD L. ALT.—Dr. Wolff has learned very well the language of the hematologist. His paper is an excellent review of the fundamentals of hematology and should help greatly in solving some of the hematologic problems that occur during pregnancy.

As a routine procedure, the sternal puncture should not be done before the patient is adequately worked up. In most cases, a diagnosis can be made from the history, physical examination, and a complete study of the peripheral blood picture. If then there is a question as to the exact diagnosis, the sternal marrow will often give the additional information needed.

I should like to emphasize the wide variations in the red count and hemoglobin value that occur in normal adults. Similar variations occur during pregnancy, but at a 20 per cent lower range. Thus a red count of 3.5 million and hemoglobin of 10 Gm. in a pregnant woman is at the lower limit of normal. Sternal marrow studies may give valuable information in patients with borderline counts. Whereas the normal myeloid-erythroid ratio does not run below 3 to 1, the proportion of normoblasts is higher in patients after hemorrhage or with iron deficiency.

Several years ago, I discussed before this Society a paper by Dr. Grier on acute leukemia occurring in the sixth month of pregnancy. Since then I have seen another similar case in the fourth month of pregnancy. The patient died a month and a half later. Occasionally, it is possible to keep such patients alive with blood transfusions until the fetus becomes viable. Problems come up in treating leukemia in pregnancy which never occur in the nonpregnant cases.

Another case of interest is a woman, seen in 1932, with a familial hemolytic anemia. Splenectomy was refused at that time. She became pregnant eight years later, and when seen after three months, had a rather marked anemia. Splenectomy was performed at this time without interference with the pregnancy. The blood count returned to normal and her subsequent course and delivery were uneventful.

The effect of pregnancy in stimulating myelopoiesis is brought out by another patient. For a period of six months, she had a leucocyte count of 2,500 to 3,500, with an average of 15 to 20 per cent neutrophilic granulocytes. The erythrocyte and thrombocyte counts were normal. Sternal puncture showed a slight drift to the left in the myeloid cells. Two months after becoming pregnant, the leucocyte count was 5,000, and the differential count was normal.

The last case I wish to mention is one that we have reported in the literature. A woman, six months pregnant, developed a typical catarrhal jaundice. Two weeks later the platelets disappeared from the peripheral blood and a typical purpura occurred. As the jaundice cleared up, the platelets gradually increased. She delivered seven weeks prematurely when the platelets were back to 75,000. There was no excessive bleeding during or after delivery. It has been pointed out previously that women with hemorrhagic disease get along surprisingly well during labor, though they may have trouble after delivery.

The above cases illustrate some of the hematologic problems that arise during pregnancy. A study of the sternal marrow is often of considerable help in making the diagnosis and planning treatment.

DR. WOLFF (Closing).—Dr. Schmitz questions the technique of obtaining and analyzing the bone marrow fluid. Limarzi has performed bone marrow analysis via sternal puncture as described in over 2,700 patients. The findings obtained in both health and disease are well known. We have used this method in over two hundred women during various intervals of their pregnancy. In our hands the technique seems to be simple and yields accurate results.

We have not made a thorough study of iron deficiency anemia per se. While determining the correlation of the peripheral blood and bone marrow findings in a group of

normal healthy women during pregnancy, we encountered cases of iron deficiency anemia and have reported the findings in these patients. Thus we have no statistics to present on the incidence of this type of anemia during pregnancy. However, we do feel that these iron deficiency anemias are not quite as prominent as reported by some investigators. Our patients are all of the low income clinic variety, and we do not find too many with this hypochromic anemia.

We feel that iron medication does not have any prophylactic value during pregnancy. It is only of value in the true hypochromic anemias. Iron medication itself may do harm since it often leads to nausea and other gastrointestinal disturbances.

As to routine sternal aspiration, it is necessary only in the anemic patients or those having symptoms suggestive of a blood dyscrasia. We have a rule in our clinic that when the hemoglobin is below 70 per cent, the patient is referred to the hematology department. A complete study of the peripheral blood is made. If the patient is found to be anemic, then a sternal marrow puncture is performed. It is thus a routine procedure on the anemic patients.

May I thank Dr. Alt for his kind remarks. Yes, we have found only scant reference to sternal punctures during pregnancy. We feel that this study has been neglected. We feel that both the hematologist and the obstetrician may obtain important clinical information from this study of the bone marrow.

STUDIES ON THE RED FLUORESCENT PORPHYRIN DEPOSITS ON VAGINA AND CERVIX

A Possible Aid in the Detection of Malignancy

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PORPHYRIN, in combination with iron (heme), forms the active part of such molecules as cytochrome-c, hemoglobin, peroxidase, catalase, and myoglobin.^{1, 6, 15, 16} In the form of these metal complexes, they are therefore present in all cells, including bacteria, yeasts, and cells of higher animals. There are many types of porphyrin, but the most common one in tissues of the human subject is protoporphyrin-9, which is the basic nucleus of hemoglobin after iron and globin have been removed.^{1, 6} The normal degradation of hemoglobin in the liver probably does not result in the formation of protoporphyrin, but the iron porphyrin ring is opened up before the iron is removed.¹¹ Free porphyrins are red fluorescent in near ultraviolet light. It has been previously demonstrated^{4, 9} that porphyrins are frequently present on the female genitals in amounts sufficient to cause a red glow when examined in this light (Wood's) in a darkened room.

The present interest in the relation of porphyrins to gynecologic problems stems from the postulate that there may be etiologic factors preceding, and sometimes accompanying, the development of carcinoma of the cervix. The previous work which supported this hypothesis^{3, 4, 9} led to the supposition that the presence of porphyrins may, on occasion, lead us to suspect a carcinomatous lesion of the uterus which would not be detected otherwise. In the present survey, we have determined the normal incidence of this red fluorescent material in its relation to the menstrual cycle. This study indicates that the presence of porphyrins cannot be used to detect early stages of cancer, to the exclusion of the other methods.

In 1942, Figge and Strong² observed that cancer-susceptible strains of mice maintained on a Nourishmix diet possessed red fluorescent harderian glands. The harderian glands of cancer-resistant strains of mice were not red fluorescent. This led to the hypothesis that there might be a direct or indirect relationship between these substances and the development of malignancy. Later, Figge³ correlated this same fluorescence of the harderian gland of other animals with their relative susceptibility to spontaneous and induced tumors. The entire hypothesis and supporting data are published elsewhere.³ In attempting to apply this hypothesis to the human subject, a search for porphyrins in cancer-susceptible organs and tissue was initiated. This led to the rediscovery of red fluorescent deposits (porphyrin) on the female genitals.^{4, 9} In the previous studies on women, the greatest amounts of porphyrin, by far, appeared in foul lochia, where it was

shown that red fluorescent deposits (porphyrins) were sometimes present for a month or two. Obviously the fluorescent material would be pooled about the cervix uteri during most of this time. In nonputrid lochia, as well as in other conditions where purulent cervical discharge was abundant, red fluorescence often was absent. Frequently red fluorescence was found about the clitoris when not visible elsewhere on the genitals. It was noted also that in some women the red fluorescent deposits were found about the vulva and vagina following the menstrual flow, but not intermenstrually. The red fluorescent material was shown to contain porphyrins, which were identified by solubility and spectrographic methods.⁴ It was thought that the porphyrin arose through the action of certain bacteria on blood or other cellular elements, but other possibilities were also entertained. For complete details of these studies and color photographs of the deposits on the female genitals, the reader is referred to the preceding papers.^{3, 4, 9} Hauser,⁸ who first noted red fluorescence of the genitals in 1929, also related these porphyrin deposits to the decomposition of blood acted upon by a specific bacterial flora.

The discovery of the porphyrin deposits on the female genitals strengthens the hypothesis which related porphyrin to the development of carcinoma, but certainly no actual proof of an etiologic relationship was found. It became clear that the incidence of porphyrin in normal women at various stages of the menstrual cycle should be determined before engaging in any further speculations or investigations concerning its role in the development of female genital cancer. Hence, the following planned investigations were carried out on a large group of women whom we considered as women menstruating normally. They were able and willing to cooperate in a planned procedure which would determine the presence of porphyrin postmenstrually and intermenstrually. The accumulated data were tabulated to indicate how often porphyrin occurs on the genitals of normal women, what factors govern its production, and of what diagnostic value are these red fluorescent deposits.*

Materials and Methods

1. A large group of volunteer women, patients with pulmonary tuberculosis, confined to a sanatorium, inserted a medium-sized open cone vaginal tampon of standard make on the evening of the last menstrual day. They removed the tampon and placed it in a container the following morning. The patient wrote her name, case number, and the date on the lid of the container. The tampon was examined under near ultraviolet light in a darkened room within three days before any significant decrease in fluorescence occurred. The patient avoided douches or vaginal wash until after a second vaginal tampon was used one week later; that tampon was similarly inspected for fluorescence. A rough quantitative scale was employed to indicate degrees of fluorescence encountered. Thus, small areas of dull fluorescence were indicated as traces; larger areas of weak fluorescence and minute areas of intense amounts of fluorescence were described as slight; intensely fluorescent material covering areas approximately 1, 2, 3, and 4 square centimeters of tampon surface were labeled respectively as plus 1, plus 2, plus 3, and plus 4. As a further indication of the range of this quantitative scale, it may be stated that tampons described as plus 1, probably contained at least fifty times as much porphyrin as those labeled "trace."

2. By the end of four calendar months, sufficient material had been collected to establish the normal incidence of porphyrin during the menstrual cycle. Following the tabulation of these data, further studies were carried out to rule out pelvic tuberculosis as a cause of porphyrin formation, for it is known that tubercle bacilli growing in culture are porphyrin producers and are red fluorescent. At the same time, an attempt was made to

*This study was accomplished by the cooperation of the patients and physicians of Olive View Sanatorium, with especial assistance by Dr. Ann Statz and Dr. Paul Smith.

determine the source of the porphyrins and to ascertain whether the porphyrins had caused any morphologic changes in the cervixes of those patients who consistently produced them. In addition, porphyrin analysis was made on some of the most intensely fluorescent tampons.

Limitations of the Methods

A few of the patients could not determine accurately when the menstrual period would end, and these women, for the most part, did not submit either postmenstrual or intermenstrual tampons when they were undecided about this. However, all of the patients kept an accurate calendar of their days of bleeding and the days tampons were used, so that a good cross check against error was established.

Each woman was given instructions how to insert the tampon high in the vagina so that it would rest against the cervix and posterior fornix. Obviously the success of the placement depended somewhat on the patient's manual dexterity and enthusiasm. The exact evening the patient chose as the time menstruation had been completed also must have varied somewhat between patients and between the successive periods of menstruation of any one patient. This may account for some of the differences in degrees of fluorescence between successive examinations and between individuals, for if considerable blood is collected on a tampon, the blood may quench some of the porphyrin fluorescence. Blood itself is not fluorescent. (See Fig. 1.) Additional variations were found in the bacteriologic study and will be mentioned later.

Nearly all of these volunteer women were married, younger than average age of the general population, and about one-third were nulliparous. These factors may or may not have made a difference in the fluorescence frequency found. Most of the patients were of average intelligence and were willing and able to follow instructions extremely well. However, a few were illiterate and the accuracy of their data depended on help by other patients.

Extent of the Survey

The 172 volunteer women were somewhat younger than the age for maximum carcinoma incidence. Ninety-five were between 20 and 29 years of age; fifty-nine between 30 and 39 years of age. These two age groups accounted for 90 per cent of the volunteers. There was only one patient as old as 50 years, and the youngest was 18 years of age. Most of the women had never used vaginal tampons, but very few experienced any discomfort from their use. Most of the unmarried women were, of course, excluded. Because multiparity has an important relation to carcinoma of the cervix, it is of interest to note that 56 of the patients were nulliparous, 39, primiparous, and 74, multiparous. As will be noted later, this difference seemed to have no bearing on the presence or absence of red fluorescent material. The analysis of the data collected will be summarized under three headings: i.e. (a) postmenstrual fluorescence, (b) intermenstrual fluorescence, and (c) the cause and effects of persistent intense fluorescence. The part of the investigation involving the use, collection, and examination of tampons covered a period of 4 calendar months. During that time 753 tampons were examined for fluorescence—413 postmenstrual and 340 intermenstrual.

Results

Postmenstrual fluorescence.—Postmenstrual tampons frequently showed areas of intense fluorescence (Fig. 1, d), hence it seems more advisable to indicate the number of women showing definite quantitative amounts at any time during the study, rather than to indicate the number of times any particular quantity was found on the tampons. Another reason for summary of persons rather than tampons, is that there was variation in the quantities recovered from any one person from month to month. Often the quantitative fluctuation was not great, but not infrequently it was. Some of the reasons for these differences have been enumerated under the heading "Limitation of Methods." Other factors, such as variation in the amount of menstrual flow, and changes in bacterial flora, will be discussed later. The true quantitative incidence is probably in the region of that found as the greatest amount on any one examination rather than the average amounts found on several

examinations, because the interfering factors will all tend to lower the observed quantitative amount. For example, there were only 36 women whose postmenstrual tampons averaged plus 1 or greater, but 65 volunteers (38 per cent) submitted at least one tampon which had an area of intense red fluorescence classified as plus 1 or greater; thus 102 (62 per cent) submitted tampons which showed only slight amounts or none at all. Those exhibiting fluorescence in 3 plus or 4 plus amounts (Fig. 1, *d*) probably comprise about 10 per cent of the population, for the total number exhibiting fluorescent material in these amounts during the course of study was 13. Table I will give a somewhat more detailed report of those exhibiting fairly intense fluorescence, and Fig. 1 illustrates a tampon with blood (a), and no fluorescence (b); another with some blood and much porphyrin (c), and fluorescence of plus 3 intensity (d). Briefly, the results of postmenstrual specimens may be summarized as follows: a quantity of porphyrins sufficient to saturate the surface and produce intense red fluorescence of vaginal tampons under near ultraviolet light was present postmenstrually in approximately 10 per cent of the women studied, and lesser amounts, but still sufficient to cause intense fluorescence, were found in about 40 per cent of the women. The tampons of about 60 per cent of the women studied do not exhibit more than slight amounts of red fluorescent material or none at all.

TABLE I. FLUORESCENCE OF POSTMENSTRUAL TAMPONS

GROUP	FLUORESCENCE OF POSTMENSTRUAL TAMPONS	TOTAL NO. INDIVIDUALS
(1)	0 → 2	8
(2)	$\left\{ \begin{array}{l} 1 \rightarrow 2 \\ 0 \rightarrow 3 \end{array} \right.$	13
(3)	$\left\{ \begin{array}{l} 1 \rightarrow 3 \\ 2 \end{array} \right.$	4
(4)	$\left\{ \begin{array}{l} 1 \rightarrow 4 \\ 2 \rightarrow 4 \\ 2 \rightarrow 3 \end{array} \right.$	5
(5)	4	1
Total		31

Intermenstrual fluorescence.—In order to determine whether porphyrin is present intermenstrually, the patients inserted a second tampon one week after the first tampon had been used. This second tampon not only demonstrated whether porphyrins were present through the entire menstrual cycle, but also determined whether the intermenstrual bleeding, which is frequently found at this time, will cause intense fluorescence. Rutherford¹³ found that whereas the average appearance of intermenstrual bleeding was on the 17.6 day of the cycle, microscopic bleeding was occasionally found from the fourth to the twenty-third day of the cycle. Hence, the time we chose enabled us to determine fluorescence when no normal uterine bleeding was occurring, and at the same time probably gave us a good sampling of cycles in which microscopic bleeding occurred.*

Most of the tampons collected at this time and examined under near ultraviolet light failed to show red fluorescence. This was true even when the postmenstrual tampon from the same patient had shown intense red fluorescence. However, traces or faint fluorescence was noted on 33 tampons (10 per cent, so was frequent enough to be considered a usual

*77 per cent of the patients' periods lasted 3 to 5 days, and 18 per cent 2 or 6 days, therefore, 95 per cent of the tampons were used following ninth to thirteenth day of the menstrual cycle.

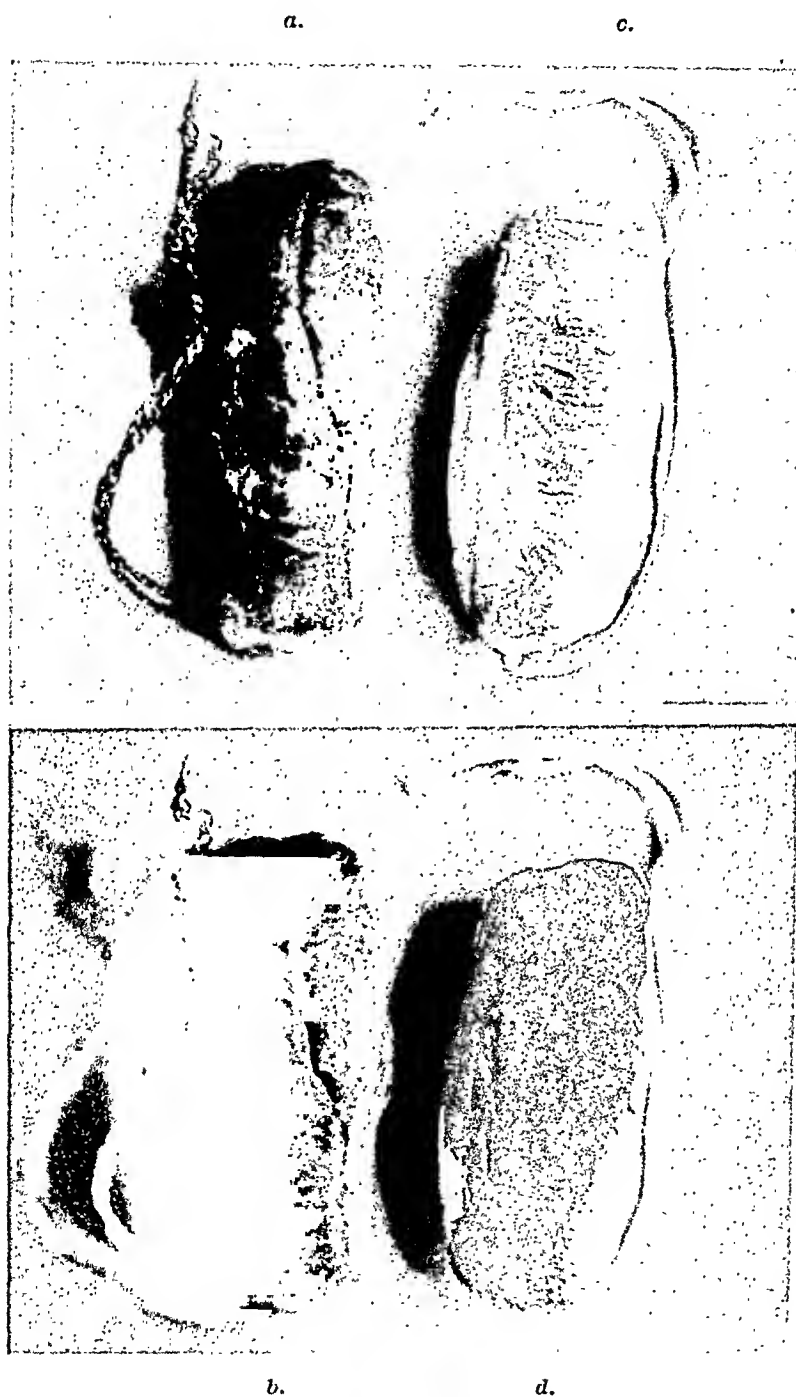


Fig. 1.—Representation in Ben Day Process of the contrast recorded on Kodachrome film between two vaginal tampons, one containing blood and no porphyrin, the other slight blood and much porphyrin.

Tampon I: Artificially treated in blood. *a.* In ordinary light this appeared red; *b.* in near ultraviolet light it appeared entirely black in conformity with the fact that blood does not fluoresce.

Tampon II: *c.* Brown stained, postmenstrual tampon in ordinary light. *d.* When illuminated with near ultraviolet light the stained areas fluoresced a brilliant red.

phenomenon). An association with intermenstrual bleeding is probable, but was not established. In addition to these tampons with pale fluorescence, there were four tampons classified as slight fluorescence, two classified as plus 1, and one identified as plus 3. One patient who submitted a plus 1 tampon left the hospital before further investigation was possible, but four of the volunteers who submitted these more intensely red fluorescent tampons were given special examinations. The data obtained are summarized below:

CASE 1.—D.D. Aged 50 years. Para iv. One intermenstrual tampon: fluorescence plus 3. Other intermenstrual tampon: 0 fluorescence. Postmenstrual tampon: slight or 0 fluorescence. This patient denied bleeding in the interval between the postmenstrual and intermenstrual tampons, but said there was bleeding for 3 days after the second tampon was used. She denied any previous intermenstrual bleeding. Pelvic examination: no pelvic abnormality except slight chronic cervicitis. Cervix biopsied: chronic inflammation and some hypertrophic changes in the cells of one endocervical gland. Repeat intermenstrual tampon two months later: 0 fluorescence. Impression: Metrorrhagia. Fluorescence probably related to imperceptible endometrial flow. Advise: Curettage if further metrorrhagia.

CASE 2.—R.S. Aged 38 years. Para i. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampon: 0 fluorescence. Postmenstrual tampon: fluorescence, slight or 0. Patient denied any intermenstrual bleeding, but stated that menstruation was scanty and prolonged, and she found it difficult to determine when menstruation ended. The postmenstrual tampon one week before had been saturated with blood. Impression: Fluorescence might be associated with imperceptible endometrial flow continuing several days after the first tampon was used.

CASE 3.—R.B. Aged 46 years. Para i. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: all showed intense fluorescence. This is one of the patients of special study, Table I. Pelvic examination: chronic hypertrophied cervix, uterine descensus, cystocele, rectocele. History of irregular and profuse menstruation. Cervix biopsied. Advise: Operation. Impression: Fluorescence probably related to imperceptible uterine flow.

CASE 4.—E.O. Aged 24 years. Para ii. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: all showed intense fluorescence. This is one of the patients of special study, Table I. Pelvic examination: no pathologic condition. Patient denied intermenstrual bleeding or irregular periods. Impression: Intermenstrual fluorescence not explained, but may be related to the regular intense postmenstrual fluorescence.

CASE 5.—A.H. Aged 22 years. Para i. Intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: fluorescence, 0 or slight. Patient denied any intermenstrual bleeding or irregularity of periods. Not examined. Impression: intermenstrual fluorescence not explained.

CASE 6.—C.O. Aged 21 years. Para i. One intermenstrual tampon: fluorescence, plus 1. Other postmenstrual tampons: plus 1, 0, 0. Periods at about 6-week intervals, lasting 5 days, but it was difficult for patient to remember dates. Denied intermenstrual bleeding. Patient not examined. Impression: intermenstrual fluorescence not explained.

CASE 7.—M.L. Aged 29 years. Para 0. One intermenstrual tampon: fluorescence, plus 1; other intermenstrual tampons: trace. Postmenstrual: plus 1 and plus 2 fluorescence. Patient left the hospital before examination was possible.

To summarize the study of these seven women: three of these patients gave evidence of possible abnormal uterine intermenstrual flow. Two others showed persistent intensely fluorescent postmenstrual tampons, and one could not be followed for further study. Three others gave no history of menstrual

irregularity, but only one of these could be examined. Because we have seen intense fluorescence intermenstrually in cancer of the uterus, we feel that the above normal incidence of moderate intermenstrual fluorescence (about 1 per cent) to be so low, that we can state, for diagnostic purposes, that *intense fluorescence intermenstrually (of the order of plus 2 or greater) should be considered an evidence of abnormal uterine flow probably associated with imperceptible bleeding which demands further study, such as curettage and biopsy of the cervix, and hence demands as much attention as visible metrorrhagia.*

In conclusion, intermenstrually, traces of red fluorescent material were present in 10 per cent of the cases and cannot be considered too unusual. However, more intense fluorescence at this time is rare. Small amounts of intense fluorescence which could not be explained were found in about 1 per cent of a series of 340 intermenstrual tampons. Therefore, it seems safe to assume that larger amounts of intense fluorescence intermenstrually are also rare.

The cause and effects of persistent intense fluorescence.—It has been shown above that intensely fluorescent intermenstrual deposits occurred in only 1 per cent of the women, whereas intensely fluorescent postmenstrual deposits occurred regularly following each menstrual period in about 10 per cent of the women. Because of the previous postulates that porphyrin is in some manner related to the development of carcinoma, this intermittent, and regular occurrence of porphyrin deposits about the cervix in some women and not in others, necessitated further study of some of these patients.

An attempt was made to determine, first, why these porphyrin deposits occurred in some women and not in others; and second, to find out whether any gross microscopic pelvic abnormalities could be discovered in porphyrin producing patients. Since the patients submitting tampons were volunteers, it was impossible to carry out extensive studies on all of the women. It was possible, however, to do a pelvic examination, culture the cervical secretion, test for pH of these secretions, and biopsy the cervix of ten women showing regular intense fluorescence and examine eleven women (as controls) whose tampons failed to show fluorescence during the months this study was conducted.

Tabulation of some of the findings of these twenty-one women may be found in Table II. In choosing the controls, many multipara were selected, for carcinoma of the cervix is about 8 or 9 times as frequent in the multiparous women as in the nulliparous.^{7, 12}

Any histologic effects produced by parity should be present in the controls as well as in those showing intense fluorescence. The pelvic examinations were carried out on a stretcher or flat table to facilitate complete exposure of the cervix in all of the speculum examinations; the cervical biopsies were taken with a punch biopsy forceps.

Since porphyrin producing bacteria are said to thrive and produce porphyrin only in alkaline media,¹⁰ it was necessary to test the cervical secretions for acidity. Nitrazine paper was used for this determination, but, as might be expected from the fact that the endocervical secretions are alkaline and the vaginal usually acid, some determinations lay on the alkaline side and some on the acid side, but there was no correlation of this with fluorescence. Because it was impossible to examine the patients without using some lubricating jelly, and in addition, because the culture media differed so widely from the vaginal secretions, the results we obtained from culture of the cervix were highly inadequate and only suggestive of the actual flora present. Cultures were plated on glucose blood agar, at reduced oxygen tension and under atmospheric conditions, and on Wallenstein's media.

Chromogenic and fluorescent colonies grew more frequently on the Wallenstein's media which is rich in egg and hence is a high porphyrin media. However, when some fluorescent *Escherichia coli* colonies were taken from this media or the glucose blood agar media, and then planted on plain agar or plain blood agar, or eosin methylin blue media, they

TABLE

NO.	NAME	TAMPONS BEFORE	AGE USED	TIMES PREGNANT	POSTMENSTRUAL FLUORESCENCE	INTERMENSTRUAL FLUORESCENCE
1	M. A.	No	25	4	2, 1	0
2	W. A.	Yes	22	1	3	0, 0
3	E. P.	Yes	34	0	2, 4, 3, 2	0, 0, 0
4	M. M.	No	36	1	3, 1, 0	Tr., 0
5	W. F.	No	24	2	3, 4	-
6	R. B.	No	46	1	4, 1, 2	Tr., Tr., Sl.
7	E. D.	No	46	3	1, 3	0
8	A. B.	Yes	20	0	2, 2	Tr., 0
9	E. M.	No	20	1	2, 2, 1	0, 0, 0
10	E. O.	No	24	2	4, 2, 1	Sl., 0, 0
1	K. G.	No	31	2	0, 0, 0, 0	0, 0, 0, 0
2	E. K.	No	25	2	0, 0	0, 0
3	A. G.	No	30	0	0, 0, 0, 0	0, 0,
4	E. F.	No	43	1	0, 0, 0	0, 0, 0
5	R. C.	No	37	2	0, 0,	0, 0
6	M. D.	Yes	29	1	0, 0, 0	0, 0, 0
7	C. R.	No	24	2	0, 0, 0	0, 0, 0
8	N. E.	No	34	11	Tr., 0, 0,	0, 0, 0
9	R. R.	No	34	3	0, 0, 0	0, 0
10	C. A.	No	36	11	0, 0	0
11	C. V.	No	36	6	0, 0	0, 0, 0

lost their fluorescence. Furthermore, it was shown that coli colonies nonfluorescent on plain agar acquired a red fluorescence when grown on Salmonella Shigella media and then again lost this fluorescence when replated on plain agar. Although this red fluorescent-acquired property from Salmonella Shigella agar media probably was not due to porphyrin, it served as a good illustration of how important the media might be in the production of fluorescence by bacteria. The media used did not duplicate well the natural media of the vagina, but fluorescent bacterial colonies did appear occasionally on the media we used. These colonies were usually one

II

EXAMINATION	CULTURE	BIOPSY
Slight eversion of cervix.	2 slightly fluorescent colonies: Actinomyces.	Many surface neutrophiles. Slight cell infiltration of stroma.
Eversion and slight chronic cervicitis.	No fluorescent colonies.	Wide cornification.
Cervix healthy (patient says she has a foul discharge 5 days after period ends).	Many fluorescent colonies: coli.	Narrow zone of round cell infiltration below squamous epithelium.
Cervix healthy.	No fluorescent colonies.	Squamous epithelium normal. No stroma present.
Chronic cervicitis.	2 tiny intensely fluorescent colonies: Staph.	Wide cornification.
Chronic hypertrophied cervix; cystocele; rectocele; uterine descensus (irreg. and profuse menstrual periods).	No fluorescent colonies.	Moderate squamous metaplasia.
Cervix healthy (was cauterized several years ago).	Very slight fluorescence of a few colonies.	Very slight squamous metaplasia.
Cervix healthy.	Many fluorescent colonies: Staph.	Squamous epithelium normal. (No stroma.)
Cervix healthy (periods last only one day).	One moderately fluorescent colony.	Extreme infiltration with neutrophiles; epithelium greatly thickened. Only slight cornification.
Cervix healthy.	Few intensely fluorescent colonies: Strep.	Squamous epithelium normal.
Cervix healthy.	No fluorescent colonies.	Neutrophiles on surface; extensive metaplasia. Wide cornification.
Cervix healthy.	1 small intensely fluorescent colony: Staph.	Wide cornification; moderate squamous metaplasia.
Much endocervical mucus.	Very faint fluorescent of few colonies.	Moderate round cell infiltration.
Few Nabothian cysts.	No fluorescent colonies.	Moderate round cell infiltration of endocervix.
Eversion of cervix and chronic cervicitis.	No fluorescent colonies.	Endocervical glands greatly dilated. Squamous epithelium normal.
Slight chronic cervicitis and Nabothian cysts.	No fluorescent colonies.	Extensive squamous metaplasia.
Cervix healthy.	Few slight fluorescent colonies (fade in 2 days): coli.	Slight squamous metaplasia.
Slight chronic cervicitis and Nabothian cysts.	Many fluorescent colonies (fade in 2 days): coli and diphtheroids.	Normal squamous epithelium.
Very slight chronic cervicitis.	No fluorescent colonies.	Slight endocervical round cell infiltration. Squamous epithelium normal.
Subacute cervicitis with a slight bleeding on examination.	No fluorescent colonies.	Tubercles, round cells and neutrophiles. Acid fast stain: tubercle bacilli.
Slight hypertrophy and chronic cervicitis. Moderate eversion.	No fluorescent colonies.	Extensive round cell infiltration of the endocervix.

specific strain of bacteria in a given individual, but several different bacteria (as shown in Table II) were isolated from the group of patients.* Furthermore, the tubercle bacilli were not grown in culture from any of the women. It may be well to point out again that in Stander's Clinic¹⁴ at the New York Hospital, the common organisms cultured from foul lochia were found to be principally anaerobic streptococci, staphylococci, and occasionally coli and diphtheroids. In the previous papers it was shown that there are large

*Dr. H. E. Pearson assisted in identifying the bacterial colonies.

amounts of porphyrin present in foul lochia, and the organisms found in this study which were productive of red fluorescence apparently are similar organisms.

The biopsies of the cervix failed to show any change which definitely could be related to porphyrin. One woman exhibiting fluorescence did show a highly proliferative squamous epithelium, but this might be caused by infection alone; furthermore, it was not a malignant lesion. One other biopsy specimen showed tuberculosis, but this was from one of the control patients.

The identity of the porphyrins extracted from the vaginal tampons.—The fluorescent portions of tampons were removed and combined because extraction of a single tampon was not practical. The method of extraction was the same as that used previously for the extraction of lochia pads.⁴ The absorption bands in 25 per cent HCl were determined by means of a Beckman Quartz Spectrophotometer. These were compared with the bands noted by other investigators and the absorption bands of synthetic porphyrins. The HCl numbers and absorption bands listed in Table III indicate that three porphyrins (coproporphyrin, deuteroporphyrin, and protoporphyrin) were extracted from the tampons. These are the same as those isolated from lochia pads. However, the absorption bands at the 0.6 per cent HCl fraction in the violet end of the spectrum indicated that this was mainly deuteroporphyrin and that little, if any, mesoporphyrin was present. Since all of these three porphyrins may be derived from protoporphyrin, they probably arose from the degradation of hemoglobin or some other heme containing cell substance.

TABLE III. ABSORPTION BANDS AND HCL NUMBERS OF PORPHYRINS EXTRACTED FROM VAGINAL TAMPONS

SOURCE OR TYPE OF PORPHYRIN	PER CENT HCL USED TO EXTRACT FROM ETHER	MAIN ABSORPTION BANDS MILLIMICROMS SOLVENT 25 PER CENT HCL			DIAGNOSIS
Tampon	0.10	592.0	550.0	405.0	Coproporphyrin
Tampon	0.60	590.0	550.0	404.0	Deuteroporphyrin
Tampon	2.00	618.0	556.0	410.0	Protoporphyrin
Coproporphyrin F.*	0.08	592.2	548.7		
Coproporphyrin S.*	0.09	593.9	550.2	405.8	
Deuteroporphyrin S.	0.40	591.0	548.0	404.0	
Mesoporphyrin F.	0.50	593.1	550.7	508.7	
Protoporphyrin F.	2.00	602.4	557.2		
Protoporphyrin S.		602.7	557.2	410.8	

*Values of Fischer and Schumm.

Discussion

The previous papers have discussed adequately the hypotheses relating cancer to porphyrin sensitization and have correlated the findings with these postulates.^{2, 4, 5, 9} There are two main questions which should be answered, i.e.: (1) are porphyrins a causative factor in the development of carcinoma of the uterus? (2) can the presence of red fluorescence be used as an aid in the diagnosis of malignancy of the uterus? The present observations as they relate to these two problems form the basis for the discussion which follows.

1. *Are porphyrins a causative factor in the development of malignancy?*—In the present study we have not been able to show that porphyrins are related to malignancy. This, however, does not mean that the porphyrin hypothesis has been disproved, for the proof of a definite relation to malignancy may be a very difficult endeavor. For example, the only two known factors that seem to be definitely related to carcinoma of the cervix are chronic infection and multiparity. The latter factor may be largely due to an estrogen effect, but there is no proof of this. In the present control series of the women

not showing fluorescence, these two factors were present, but there was no evidence of malignant change in these women either. In fact, most women subjected to these two factors do not develop carcinoma of the cervix, and in a group of women in this age distribution several thousand might be examined without finding evidence of malignant change. So, too, in proving an etiologic relationship of porphyrin to cancer, equally large series of women examined over a long period of time would be necessary for proof or disproof of this hypothesis. This is a much larger project than we have been able to carry out. The proof or disproof may be more easily accomplished by means of animal experimentation. (This is being attempted at the present time.) On the other hand, some of the findings of the present survey fit in with what we know should be required of a causative agent in the development of malignancy. From animal work with carcinogenic agents we know that their intermittent application over a long period of time may be more successful in producing tumors than a continuous application, or a short intense application. Furthermore, we know that all animals subjected to large amounts of carcinogens do not develop tumors, but it is a combination of several factors which results in malignancy. The fluorescent material found to occur postmenstrually is present in appreciable amounts in about 40 per cent of women (this is less than the incidence of either multiparity or chronic cervical infection) and in more intense amounts after every menstrual period in only about 10 per cent of women. Furthermore, it is apparent that this substance occurs intermittently over a number of years, and during the years when cancer incidence of the cervix is greatest. Moreover, it has been shown previously⁹ that additional, larger amounts may occur in postpartum women who have developed foul lochia; here the porphyrins could be agents which are synergistic with both the factor of chronic infection and parity.

2. *Can the presence of red fluorescence be used as an aid in the diagnosis of malignancy?*—In the study of postmenstrual tampons, we showed that large amounts of intensely fluorescent deposits may occur immediately following the menstrual period. Therefore, the presence of intense fluorescence at this time is not rare, and likewise cannot be used as a diagnostic aid. The biopsy of the cervix of these women showing intense fluorescence is not indicated by the presence of fluorescence alone, for we have seen that fluorescence is no indication that malignant change has been produced. Furthermore, the intermenstrual tampons demonstrated that small amounts of porphyrin may be present at this time too in 10 per cent of women. However, unexplained intense fluorescence intermenstrually is indeed rare (about 1 per cent), so that intense fluorescence at this time may be regarded as an abnormal condition and indicative of unusual uterine flow and should be regarded with as much concern as metrorrhagia. Large amounts of this red fluorescent material are sometimes found following endometrial flow, such as following menstrual bleeding, invariably found in foul lochia, and often, but not always, found in the drainage from carcinomas of the uterus.

Hence, in conclusion, we may say that if this material is present in large amounts intermenstrually it may be used as a diagnostic aid in the detection

of malignancy or any of the other causes of uterine flow. It should be emphasized, however, that early visible carcinomas of the cervix may not show porphyrin deposits, therefore, the presence or absence of porphyrins cannot be used as a test to rule out cancer. If fluorescence is to be used as a diagnostic tool, it should be used to supplement the procedures now recognized as essential, i.e., examination, biopsy, and curettage.

It is of equal importance to emphasize that no matter how small the amount of secretion in the vagina, and no matter of what color the secretions may be in ordinary light, they still may contain large amounts of intensely fluorescent material when exposed in near ultraviolet light alone, and when these porphyrins are present, the secretions are most certainly not just simple vaginal secretions. Porphyrins when present in large amounts in the vagina in the postmenopausal woman, or intermenstrually one or two weeks following the use of a vaginal tampon or postmenstrual cleansing douche in the woman still having her periods (when the examination is made one or two weeks following the use of a vaginal tampon or postmenstrual cleansing douche) should be regarded as a sign of abnormal uterine drainage and is an indication for further study to rule out malignancy. Simple lubricants which have been used in the examination will not interfere appreciably with the test. All that is required for the examination is a pledget of cotton large enough to absorb all of the vaginal secretions. After the vagina has been swabbed with this, the cotton pledget may be placed immediately (or after some hours) under the standard "black lamp" which can be kept in either a dark corner of the examining room or in a darkened room, and when this procedure is carried out the swab will instantaneously exhibit a brilliant red glow if much porphyrin is present. The test for red fluorescence (porphyrin) is thus simple, dramatic, and can easily be made an adjunct to the routine pelvic examination.

Summary

A study has been made of normally menstruating women to determine the frequency of red fluorescent (porphyrin) deposits at different phases of the menstrual cycle.

It was found that 10 per cent of the women studied showed large amounts of this red fluorescent material immediately following each menstrual period, about 28 per cent more showed fairly large amounts following one menstrual period, but not after every menstrual period, while 62 per cent of the women showed only traces or no porphyrin postmenstrually.

Culture from a swab of the cervix of some of these women showed porphyrin producing organisms of staphylococci, streptococci, actinomyces, diphtheroids, and coli. Biopsy of the cervix of a representative group of these showing red fluorescence and a control group of others not showing fluorescence, failed to demonstrate any evidence of microscopic change produced by this material.

A survey of red fluorescent deposits intermenstrually revealed that traces of red fluorescent material in the vagina are not uncommon at this interval, but intensely red fluorescent secretions are rare enough to be regarded as

abnormal. The latter finding may possibly prove to be a diagnostic aid in the detection of abnormal uterine flow, not associated with gross bleeding and the limitations and possibilities of this test are outlined. The test for this red fluorescent material is simple and dramatic, and it requires no special apparatus to determine its presence other than a standard "black lamp outfit." The test is not a substitute for examination, biopsy, curettage, or any of the tests now in use for the detection of malignancy, but may be used as an adjunct to present methods, and should aid in focusing attention on the problem of carcinoma of the uterus.

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STUDIES ON HIGH DOSAGE PROGESTERONE THERAPY OF AMENORRHEA*

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IT HAS been demonstrated by Zondek^{1, 2} that bleeding can be rapidly induced in many women with functional amenorrhea by the administration of progesterone in high dosage over a period of several days. If primary amenorrhea is present or if the secondary amenorrhea is of long duration, it is necessary to prime the uterus first with estrogen or to administer estrogen with the progesterone. Zondek and his associates have shown that progesterone withdrawal bleeding can occur from an endometrium which shows only a slight proliferative effect.^{3, 4} It can be induced soon after a normal menstrual period, but not during the normal corpus luteum phase or during pregnancy.¹ Zondek's method of treatment of amenorrhea is being widely employed because it is rapid and obviates the use of large dosages of estrogens over a long period of time with possible inhibitory effect on the anterior pituitary.

It is probable that the initial bleeding after the administration of progesterone results from the direct effect of the hormone on the endometrium. However, that progesterone may have a more important effect on the sex-endocrine mechanism is indicated by the fact that in some of the patients one or more spontaneous bleedings will occur following the discontinuation of treatment, and during this interval it is occasionally possible for a pregnancy to occur.¹ It is these latter observations which add considerable weight to the importance of high dosage progesterone therapy and indicate the desirability of further investigation of the underlying endocrine mechanism.

To shed further light on various phases of this problem, we carried out the following types of clinical investigation:

1. An evaluation was made of the endocrine status of the amenorrheic patients to be treated. In addition to clinical observations, hormone assays for estrogens, gonadotrophins and 17-ketosteroids were made by methods previously published from our laboratory.⁵ Vaginal smears for cytologic study were also taken, and in selected cases endometrial biopsies were obtained.

2. High dosage progesterone alone was the initial treatment given to these patients in almost all instances. Generally, this therapy consisted of the intramuscular injection of 20 mg. of progesterone on each of three consecutive days. When this type of treatment failed, the patients were primed with small amounts of estrogens orally for one to two weeks, and then the progesterone was repeated. Occasionally, the estrogen was given in high dosage by injection.

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tion along with the progesterone as recommended by Zondek;² usually we gave 10,000 rat units of alpha-estradiol benzoate and 20 mg. of progesterone at each injection.*

3. In selected cases, hormonal assays and endometrial biopsy were repeated during the course of treatment and at intervals following therapy. Vaginal smears were made frequently on all cases.

The pertinent clinical data of the amenorrhea cases studied are summarized in Tables I, II, and III.

TABLE I. PATIENTS STUDIED

Number of patients	51
Age range	18-36
	18-25=34 patients
	26-36=17 patients
Marital status	
Single	21
Married	30
Fertility	
Primary sterility problem	20
Child sterility	2
Undetermined	8

TABLE II. TYPE OF AMENORRHEA AND DURATION

Primary	7
Secondary	44
Duration of Secondary Amenorrhea	
More than 2 years	
2 to 13 years	19
1 to 2 years	5
6 months to 1 year	14
Less than 6 months	6

TABLE III. ENDOCRINE STATUS

	PRIMARY AMENORRHEA	SECONDARY AMENORRHEA	TOTAL
Gonadotropic deficiency	2	16	18
Primary ovarian deficiency	4	24	28
Adrenogenital syndrome		4	4
Endometrial defect	1		1

•Primary Amenorrhea

There were 7 patients with primary amenorrhea (Table IV) varying in age from 18 to 25.

Gonadotropic Deficiency.—In two of these cases there was a gonadotropic deficiency as indicated by absence of gonadotropic hormone in the urine and diminished estrogens. In neither of these cases was it possible to induce bleeding by the cyclic administration for three months of pituitary gonadotrophins or a combination of pituitary and chorionic gonadotrophins (Synapoidin). In one of these patients the gonadotrophin was followed by 20 mg. of progesterone on three successive days without effect. These observations suggest that in these patients the ovaries may be incapable of stimulation by gonadotrophins. Cyclic bleeding was finally induced in one of these patients by priming with

*The following hormones were supplied through the courtesy of Dr. Max Gilbert of the Sehering Corporation, Bloomfield, New Jersey: ampoules of Progynon-B (alpha-estradiol benzoate), ampoules of Proluton (Progesterone), tablets of Pranone (anhydro-hydroxy-progesterone and tablets of Estinyl (ethinyl-estradiol).

TABLE IV. PRIMARY AMENORRHEA

	GONADOTROPIC DEFICIENCY	PRIMARY OVARIAN DEFICIENCY	UTERINE DEFECT	TOTAL
Number of patients	2	4	1	7
Bleeding after pro- gesterone alone	0	0	0	0
Bleeding after estrogen and progesterone	1			5 of 6
Subsequent spontaneous bleeding	1 not treated	4	0	treated
Had 3 or more sponta- neous cycles	0	1	0	1
Became pregnant	0	0	0	0
	0	0	0	0
	(neither married)	(one married)		

estrogen and following with 60 mg. of progesterone. Either estrogen or progesterone alone failed to produce a result, nor was it possible to successfully reduce the progesterone to less than 20 mg. (10 mg. on successive days); furthermore, after a number of bleedings had been successfully induced, the ovaries still remained refractory to further gonadotropic stimulation. Hormone assays made at intervals after treatment failed to show gonadotrophins and estrogens in the urine. The second of these patients also failed to respond to progesterone in full dosage and has not yet been given the combined therapy.

Primary Ovarian Deficiency.—Four of the patients with primary amenorrhea proved on hormone assays to have a primary ovarian deficiency as indicated by excessively high gonadotrophin excretion with diminished estrogens.

Two of these patients presented distinctly eunuchoid features:

G. A., aged 24 years, had failed to bleed when treated at various times previously with estrogen or after one course of low dosage x-ray to pituitary and ovaries. The first menses was induced by priming with 0.5 mg. of stilbestrol for two weeks and following with injections of 20 mg. of progesterone on three days. This was successfully repeated on several occasions, but failed whenever the progesterone was reduced to less than 20 mg. (10 mg. twice). Sixty mg. of progesterone given without estrogen priming also failed. Although full development of the secondary sex characters occurred during the course of treatment, there was no improvement in subsequent hormone assays. The uterus remained infantile, and no endometrium could be obtained by biopsy.

G. H., aged 19 years, failed to bleed after 60 mg. of progesterone (20 mg. on three successive days) but had a good flow when this dosage was preceded by priming with 0.1 mg. of ethinyl estradiol daily for three weeks. After four such courses, similar bleeding was induced by substituting for the injections of progesterone, oral administration of 100 mg. of anhydro-hydroxy-progesterone daily for three days. This was followed by one spontaneous period without any therapy. During this month moderate amounts of both gonadotrophins and estrogens were present in the urine on two assays. The following month, the patient reverted to amenorrhea with progressive diminution in gonadotrophin and estrogen. Subsequently, it was possible to induce bleeding with 60 mg. of progesterone alone but not with 300 mg. of the oral preparation.

Two patients in this group were typical examples of the syndrome described by Varney and co-workers,⁶ and Albright and associates.⁷ These were of short stature, had sexual infantilism, and high gonadotrophins.

B. G., aged 23 years, had been treated previously with pregnant mare serum gonadotrophins without success. Injections of 60 mg. of progesterone over three days failed to produce bleeding. Initial priming with 0.5 mg. of stilbestrol for three weeks, followed by progesterone in the same dosage, resulted in a good flow. The progesterone was then successfully given alone in the same dosage, and then gradually reduced each month. Bleeding could not be induced when the progesterone was lowered to less than 20 mg. given in one or two injections. A total of 24 bleedings were induced. No spontaneous menses

occurred. The only hormonal change noted was a moderate reduction in the gonadotrophin titer in the cycles following progesterone administration. During the course of treatment sexual maturation occurred, but the small uterus did not grow appreciably.

H. B., aged 19 years. The first menses was induced by priming with stilbestrol for two weeks followed by 6 mg. of progesterone. Attempts to produce bleeding with the progesterone alone were unsuccessful, although it was possible to later induce bleeding with 60 mg. of progesterone after three periods had been induced with combined therapy. On one occasion the patient spotted spontaneously, but has shown no tendency to continue to cycle without treatment. There was a rapid development in secondary sex characters during the course of treatment. There was no improvement in the hormonal picture, the gonadotrophins remaining high and the estrogens nondemonstrable.

There was one patient with normal sexual development but diminished estrogens and moderately high gonadotrophins. This patient, R. A., aged 18 years, also failed to bleed after full dosage of progesterone (60 mg.), but did respond after estrogen priming. Eventually, bleeding could be induced by 10 mg. of progesterone alone, but no spontaneous flow occurred. On several occasions during treatment with progesterone alone, low normal estrogen values were obtained in the urine and by vaginal smear.

Uterine Defect.—One patient had primary amenorrhea due to a primary endometrial defect. L. B., aged 25 years, had well-developed secondary sexual characteristics, but an extremely infantile uterus since she was 13 years of age. Preliminary hormone assays showed normal titers of estrogens and gonadotrophins in the urine which appeared to show cyclic fluctuations.

Progesterone in a dosage of 60 mg. failed to induce bleeding. Preliminary priming with stilbestrol followed by progesterone also failed on four occasions to induce bleeding, even when the stilbestrol was given in a dosage of 2 mg. daily for 6 weeks before progesterone. Curettage showed a minute uterine cavity with just a small bit of polypoid tissue which, on histologic examination, showed a few atrophic endometrial glands. The vaginal biopsy taken at the same time also showed atrophic changes indicating the defect probably involved other Müllerian derivatives. On endometrial biopsy after administration of high dosage of estrogen, no tissue could be obtained.

Secondary Amenorrhea

There were a total of 44 patients with secondary amenorrhea. Results of treatment will be discussed both with regard to the duration of the amenorrhea and the type of endocrine defect.

Diminished Gonadotrophins (Table V).—

Secondary amenorrhea for more than 2 years: There were 7 patients in this group. It was possible to induce initial bleeding with progesterone alone (20 mg. by injection for 3 days) in only two of these patients. After inducing several bleedings with gradually

TABLE V. SECONDARY AMENORRHEA

	GONADOTROPIC DEFICIENCY		TOTAL
	MORE THAN 2 YEARS	LESS THAN 2 YEARS	
Number of patients	7	9	16
Bleeding after progesterone alone	2	8*	10
Failed with progesterone alone	5	1	6
Subsequent spontaneous bleeding	2	6	8
Had 3 or more spontaneous cycles	2	3	5
Became pregnant	1	0	1
Bleeding after estrogen priming + progesterone	5	1	6
Failed with estrogen priming + progesterone	0	0	0
Subsequent spontaneous bleeding	2	1	3
Had 3 or more spontaneous cycles	2	1	3
Became pregnant	1	0	1
	(miscarried)		

*Two treated unsuccessfully with 300 mg. anhydro-hydroxy-progesterone orally over 3 days.

reduced dosages of progesterone, both patients began to have spontaneous flows and one patient became pregnant.

M. V., aged 27 years, had been under treatment in our sterility clinic for ten years because of secondary amenorrhea and sterility. The gonadotrophins were consistently absent in the urine, estrogens diminished, and the endometrium atrophic. Treatment with low dosage x-ray to pituitary and ovaries had induced occasional periods after the first two courses of treatment, but later no response was obtained. The patient had responded to various gonadotrophins for short periods and then became refractory. After a period of amenorrhea of two years, bleeding was induced with 60 mg. of progesterone. After four periods had been induced, the patient had three spontaneous flows and then became pregnant. Estrogen and progesterone therapy were continued throughout pregnancy and she was delivered of a full-term, normal baby.

All of the 5 additional patients menstruated after preliminary priming with estrogen followed by progesterone. Two of the patients menstruated spontaneously for more than 6 months after several bleedings had been induced with subsequent injections of progesterone alone, and one patient became pregnant during this interval, but miscarried at 3 months. Two additional patients had induced bleeding with progesterone alone even in dosages of 20 mg., but had no spontaneous periods. One patient had bleeding only when the progesterone and estrogen were continued, but would fail with either alone.

Secondary amenorrhea for less than 2 years: There were 9 patients with secondary amenorrhea of less than 2 years' duration associated with diminished gonadotrophin and estrogen excretion in the urine.

Seven of these patients received a course of progesterone alone (30 to 60 mg. over 3 days) and bleeding occurred in six. After inducing several menses, three of these patients menstruated spontaneously from three to six months or more, while the other three patients had occasional spontaneous periods after bleedings which were induced with a single injection of 20 mg. of progesterone. The patient who failed to respond at all to progesterone alone had an associated anorexia nervosa. Bleeding could be induced in this patient only with preliminary estrogen priming, which resulted in a marked beneficial psychic effect, resultant gain in weight, and later, spontaneous menstruation.

Another patient in this group had been treated with pituitary and chorionic gonadotrophin (Synapoidin) prior to progesterone, and had responded with three cyclic episodes of bleeding, but later became refractory to this treatment and subsequently responded to progesterone.

Two patients were treated with 300 mg. of anhydro-hydroxy-progesterone alone by mouth and failed to respond with bleeding, but did respond subsequently to 60 mg. of progesterone and later to smaller dosages. Spontaneous bleeding did not occur in either of these cases.

Primary Ovarian Deficiency (Table VI).—

Secondary amenorrhea for more than 2 years: There were 9 patients with secondary amenorrhea of more than 2 years' duration who had developed a primary ovarian deficiency as indicated by high urinary gonadotrophins and diminished estrogens.

TABLE VI. SECONDARY AMENORRHEA

	PRIMARY OVARIAN DEFICIENCY		TOTAL
	MORE THAN 2 YEARS	LESS THAN 2 YEARS	
Number of patients	9	15	24
Bleeding after progesterone alone	1	14	15
Failed with progesterone alone	8	1	9
Subsequent spontaneous bleeding	1	11	12
Had 3 or more spontaneous cycles	0	9	9
Became pregnant	1	3	4
Bleeding after estrogen priming + progesterone	8	1	9
Failed with estrogen priming + progesterone	0	0	0
Subsequent spontaneous bleeding	3	0	3
Had 3 or more spontaneous cycles	0	0	0
Became pregnant	0	0	0

Only one patient of the nine responded with bleeding following progesterone alone in full dosage (60 mg. in 3 days). A. H., aged 25 years, with secondary amenorrhea for two and one-half years' duration, cycled spontaneously after several periods were induced with progesterone alone, and within two months became pregnant and carried to term. During pregnancy she was treated with large dosages of estrogen and progesterone.⁹ She had previously miscarried twice.

Another patient had one period with progesterone after the initial period was induced with estrogen, and then failed to respond to further progesterone. S. S., aged 36 years, had amenorrhea of 3 years' duration, hot flashes, and an atrophic vaginal smear. After Premarin daily for 21 days she had estrogen withdrawal bleeding. The following month one flow occurred after the administration of 60 mg. of progesterone. The patient failed to respond to further progesterone therapy without initial estrogen priming.

The additional patients all responded with bleeding when primed with estrogen before repeating the progesterone. Three of these were able to continue with progesterone alone and had occasional single spontaneous cycles; then lapsed into amenorrhea unless progesterone was again given in amounts of 20 mg. or more. Urine hormone assays frequently showed improved estrogen excretion during the course of progesterone therapy. Endometrial biopsies made in two cases late in the cycle following progesterone showed an estrogenic type of endometrium with no secretory changes. The remaining five patients in this group required some estrogen priming before progesterone, although the dosage of the latter could generally be reduced to 20 mg. Best results were obtained when the latter was given as 10 mg. on two successive days. There were four patients in this group who were sterility problems; none became pregnant.

Secondary amenorrhea of less than 2 years' duration: There were a total of 15 patients in this group. Fourteen responded with bleeding to an initial course of progesterone, 30 to 60 mg. over a period of 3 days. After several periods were induced in this fashion with gradually diminishing dosages of progesterone, nine patients had three or more spontaneous menstrual cycles or became pregnant. Pregnancy occurred in three instances, and all three patients went to term, although all received additional estrogen and progesterone during early pregnancy.

The additional six patients required progesterone in amounts of 10 to 30 mg. in order to induce bleeding, and only an occasional spontaneous bleeding occurred.

One patient, B. T., aged 24 years, with secondary amenorrhea for six months and a history of similar episodes earlier, failed to respond to progesterone alone. After priming with ethinyl estradiol and then giving progesterone, three bleedings were induced. No spontaneous cycles followed withdrawal of therapy. This patient had an infantile uterus, and it is probable that in addition to hypogonadism, the endometrium was poorly responsive.

Adrenogenital Syndrome (Table VII).—Four patients with secondary amenorrhea were classified after study as probably having an adrenogenital syndrome. These patients, in addition to amenorrhea, showed marked hirsutism and obesity. Estrogens and gonadotrophins were repeatedly present in the urine in amounts within the normal range. The 17-ketosteroids were in the high normal range in three instances and moderately high (24 mg.) in one case. There was no positive evidence indicating an adrenal cortical tumor or a Cushing's syndrome in any of these cases.

TABLE VII. SECONDARY AMENORRHEA
ADRENOGENITAL SYNDROME

	MORE THAN 2 YEARS	LESS THAN 2 YEARS
Number of patients	2	2
Bleeding after progesterone	2	2
Failed with progesterone alone	0	0
Subsequent spontaneous bleeding	1	0
Had 3 or more spontaneous cycles	1	0
Became pregnant	0	neither
	1 married	married

Bleeding was induced in all four patients following the injection of progesterone in a dosage of 30 to 60 mg. over three days.

In one instance, F. N., aged 28 years, three spontaneous bleedings occurred. The endometrium in this case which prior to treatment was of the early interval type, showed late secretory changes in the cycle following progesterone therapy. This patient, who was a sterility problem, did not become pregnant.

Progesterone in dosage of 10 to 30 mg. was required to induce further bleeding in the three remaining cases.

Summary of Results of Treatment in Various Groups

In Table VIII there is summarized results of treatment with high dosage progesterone with and without estrogen priming, the relationship of the type of amenorrhea, the hormonal status of the patient, and the duration of the amenorrhea. It will be noted that bleeding was eventually induced in 49 of the 51 patients. In 29 cases, or 57 per cent, bleeding occurred following high dosage progesterone alone, while in 20, or 95 per cent, of the remaining 21 cases treated, bleeding occurred when estrogen was added to progesterone therapy. Subsequent spontaneous bleeding occurred in a total of 29, or 57 per cent, of the cases but only 19, or 37 per cent, had three or more spontaneous cycles. A total of 8, or 27 per cent, of the 30 married women in this group became pregnant, and all carried to term except one.

TABLE VIII. SUMMARY OF RESULTS

	TYPE OF AMENORRHEA		HORMONAL STATUS*		DURATION		TOTAL GROUP
	PRIMARY AMENORRHEA	SECONDARY AMENORRHEA	GONADOTROPIC DEFICIENCY	PRIMARY OVARIAN DEFICIENCY	MORE THAN 2 YEARS	LESS THAN 2 YEARS	
Number of patients	7	44	18	28	25	26	51
Bleeding after progesterone	0	29	10	15	5	24	29
Subsequent spontaneous bleeding		21	8	12	4	17	21
Had 3 or more spontaneous cycles		15	5	9	2	12	15
Became pregnant		5	1	4	2	4	6
Bleeding after estrogen priming + progesterone	5 of 6 treated	15	8	13	18	2	20
Failed with estrogen priming + progesterone	1	0	0	0	1	0	1
Subsequent spontaneous bleeding	1	6	3	4	7	1	8
Had 3 or more spontaneous cycles	0	3	3	0	3	1	4
Became pregnant	0	1	1	0	2	0	2

*In addition there were 4 patients with adrenogenital syndrome and one with primary uterine defect.

High Dosage Progesterone as a Clinical Test for Pregnancy in Patients With Recent Amenorrhea

We treated 18 young women with delayed menstruation of only two weeks to three months' duration. In all of these cases, a question of pregnancy arose which was checked by the Friedman test. At the same time, these patients were started on 20 mg. of progesterone on each of two or three successive days. The results are given in Table IX. In 17 of the 18 cases, pregnancy or its absence was properly indicated by the clinical results; i.e., whether or not bleeding was induced within three to five days after the last injection. In one patient who received 40 mg. of progesterone after two weeks of amenorrhea, no bleeding occurred for five weeks. It is probable that this patient at the time of injection

TABLE IX. HIGH DOSAGE PROGESTERONE AS A CLINICAL TEST FOR PREGNANCY

	PATIENTS	WITH-DRAWAL BLEEDING	FRIED-MAN TEST NEGATIVE	NO BLEEDING	FRIED-MAN TEST POSITIVE
Progesterone 40 mg. (20 mg. on 2 days)	8	5	5	3*	2
Progesterone 60 mg. (20 mg. on 3 days)	10	6	6	4	4
Total	18	11	11	7	6

*In one of these bleeding finally occurred after three weeks.

was in the corpus luteum phase of a delayed cycle, since Zondek,¹ has shown that progesterone will not produce bleeding during this phase. Zondek has also indicated, and it has frequently been corroborated by us, that progesterone and estrogen in the dosage used in the treatment of amenorrhea will have no harmful effects upon a normal pregnancy.

As a clinical procedure in patients with suspected pregnancy, high dosage progesterone therapy is of value because it will usually induce bleeding promptly in patients who are desirous of having a menstrual flow if they are not pregnant.

Discussion

High dosage progesterone therapy has proved to be a valuable adjunct in the treatment of functional amenorrhea. When used alone in patients with recent amenorrhea, it will usually induce bleeding, while when used in conjunction with estrogens, bleeding can regularly be induced except in those rare instances where there is an associated uterine defect or if the woman is pregnant. Even the patient with primary amenorrhea can be made to bleed, although invariably this requires priming with estrogen and full dosage of progesterone or the simultaneous injection of both. However, the patients with primary amenorrhea will rarely have a spontaneous bleeding even after repeated induced flows, while a proportion of these will have one or more spontaneous flows, particularly if their amenorrhea is of recent origin. These observations confirm those originally made by Zondek.

Our studies further indicate that these results may be expected in patients with various types of sex-endocrine dysfunction. In patients with primary amenorrhea, whether due to a gonadotrophic deficiency or, as is more common, due to a primary ovarian deficiency, estrogen is required to obtain bleeding with full dosages of progesterone. Zondek early pointed out that at least minimal amounts of estrogen must be present to obtain a reaction with progesterone, but that even this minimal amount is apparently not present in women with true primary amenorrhea. In the cases of secondary amenorrhea, a high percentage of good results can be expected with progesterone alone whether the patient has a primary gonadotropic or primary ovarian deficiency, provided the amenorrhea is of less than two years' duration, whereas, in both groups, if the amenorrhea is of longer duration, additional estrogen is required. This is of especial interest in that estrogen deficiencies, as determined by urinary hormone assays, vaginal smears, and endometrial biopsy were equally marked in most members of both groups. This raises the question as to whether the uterus becomes increasingly refractory as the amenorrhea persists. Further investigations on castrate women are under way to determine this point. On the other hand, in the patients in whom the amenorrhea was asso-

ciated with good urinary estrogen values (believed to have an adrenogenital syndrome) bleeding occurred with progesterone alone despite the duration of amenorrhea, which in one case was of 10 years' persistence. This latter group constitutes an exception to the generalization that amenorrhea of more than two years' duration requires administration of estrogen in addition to progesterone to induce bleeding.

The study of the urinary hormone assays following progesterone, or estrogen plus progesterone, indicates that an improvement in the hormonal pattern is noted in many instances of secondary amenorrhea, whether caused by a gonadotropic or primary ovarian deficiency. In the former group, there is frequently an increase in the gonadotrophin and estrogen titer, particularly in the month or two following injection, and is no doubt responsible for the spontaneous cycling in some of these patients, and for the improvement in the endometrial biopsy as well as the occasional pregnancy. This at first suggests that progesterone may have a favorable "back-action" on the pituitary. Such an hypothesis is hardly supported by our knowledge of progesterone physiology. In many species, estrogen is believed to suppress the follicle stimulating function of the pituitary and under certain conditions to promote the release of luteinizing hormone,¹⁰ while progesterone suppresses the release of luteinizing hormone;¹¹ whether this in turn may be followed by a release of the follicle-stimulating hormone in women under the conditions in which it is here employed is not known, but certainly requires further study.

In women with a primary ovarian hypofunction, the majority of our hormonal findings seem to indicate an entirely different mechanism. Here the primary change seems to be an improved estrogen excretion following high dosage progesterone therapy, even in those instances in which estrogen was not given in the previous cycle; frequently, but not always, there was a reduction of high gonadotrophin levels to more nearly normal values. These findings suggest that the ovary has become more responsive to gonadotropic stimulation. In this regard, it is of interest that the patients in this group who had amenorrhea of more than two years' duration or who had frank menopausal symptoms were less likely to show this type of improvement or to menstruate spontaneously. It is of interest, however, that one young woman in this group did have two spontaneous cycles, became pregnant, and carried to term. Such observations suggest that there is a profound difference between the ovary of the young woman with a temporary primary ovarian deficiency and a patient with a frank menopausal syndrome, despite the similarity in their hormonal patterns.

Our observations in patients believed to have an adrenogenital syndrome are not sufficient to draw any conclusions concerning the mechanism of bleeding. Probably the large amount of progesterone administered reduces the total estrogenic effect with resultant withdrawal bleeding. Such a theory would explain why three of our patients in this group failed to cycle spontaneously at any time; however, one patient in this group not only cycled spontaneously three times, but, on one occasion at least, developed a typical secretory endometrium.

Our clinical and laboratory studies have led us to believe that high dosage progesterone therapy has a distinct place in the treatment of certain types of impaired fertility in the female, especially when associated with hypomenorrhea or secondary amenorrhea. When the condition is associated with gonadotropic deficiency, stimulation therapy with gonadotropic hormone is generally the treatment of choice. The difficulties attendant upon the prolonged continuation of such treatment, particularly because of the possibility of producing cystic ovaries¹² or antigonadotrophins¹³ often make it expedient to change to progesterone after three months on gonadotropic hormone. In primary ovarian deficiencies in young women, high dosage progesterone would appear to be the treatment of choice since it obviates the use of prolonged estrogen therapy which, during the time of administration, would certainly tend to inhibit ovulation. Finally, in the young sterile women with amenorrhea or hypomenorrhea, the induction of regular bleeding episodes avoids much psychological trauma when the patient is anxious to believe that she may be pregnant. If pregnancy does occur, this type of therapy does not prove harmful as shown by Zondek¹ and by our observations; indeed, the failure to bleed arouses suspicion that pregnancy has occurred.

Summary

1. A total of 51 amenorrheic patients were treated with high dosage progesterone with or without additional estrogen. Seven of the patients had primary amenorrhea, while in 44 of the cases, secondary amenorrhea was present. In 25 of the cases the amenorrhea was of more than two years' duration. From the endocrine standpoint, 18 of the patients had gonadotropic deficiencies, 28 of the patients had a primary ovarian deficiency. Four patients were believed to have an adrenogenital syndrome, and one patient had a primary uterine defect.

2. In the 25 patients with amenorrhea of more than two years' duration, only 5, or 25 per cent, responded with bleeding to progesterone alone, whereas 24, or 92 per cent, of the 26 patients with amenorrhea of lesser duration bled.

3. None of the patients with primary amenorrhea had bleeding after 60 mg. of progesterone, while 5 of the 6 who were given progesterone after estrogen priming had induced bleeding. Only one spontaneous bleeding occurred after withdrawal therapy. The patient who failed to respond at all had an endometrial defect.

4. Of the 44 patients with secondary amenorrhea, 29, or 66 per cent, responded to progesterone alone. Many of these had subsequent spontaneous bleedings, and five became pregnant. The remaining 15 patients had induced bleeding with progesterone after estrogen priming. A smaller percentage of these patients had subsequent cycles and only one became pregnant.

5. The patients with a gonadotropic deficiency and a primary ovarian deficiency responded approximately equally well so far as induction of bleeding was concerned. In both of these groups there was a tendency for the hormonal status to improve immediately following treatment as indicated by

increased gonadotropic production in the first group and better ovarian response (increased estrogens and improved endometrium) in the second group.

6. Four patients with secondary amenorrhea due to adrenogenital syndrome responded with bleeding to progesterone therapy alone, even if the amenorrhea was of long duration. The endocrine status of these patients did not improve.

7. Eight (27 per cent) of the 30 married women became pregnant following therapy.

8. An additional group of 18 patients with delayed menstruation or recent amenorrhea who were suspected of pregnancy were treated with 40 to 60 mg. of progesterone, 20 mg. on two or three successive days. As checked by the Friedman test, bleeding failed to occur if pregnancy was present, whereas in all but one instance bleeding was induced in the nonpregnant patients.

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Discussion

DR. ARTHUR FIRST.—From a practical standpoint, Dr. Rakoff's interesting paper brings up the important question—does progesterone afford us a worth-while addition to our therapeutic armamentarium in the treatment of amenorrhea? I think Dr. Rakoff's studies show that in many instances it does, especially in an estrogen primed endometrium.

Even the advisability of treating amenorrhea is a controversial subject today. Take for example Greenhill's statement in the 1944 *Year Book of Obstetrics and Gynecology* to the effect, "I am opposed to treating amenorrhea except in young girls who have not begun to menstruate by the time they reach 18 and in married women who desire children. I see no reason at all to treat women who have scanty menstruation or infrequent menses. I think they are fortunate in losing only a small amount of blood."

In spite of this, I agree with Dr. Rakoff when he cites the "psychological trauma" of these amenorrheic individuals. I also believe that, untreated, the endocrine deficiency may ultimately result in permanent damage to the ovaries and uterus.

It must be admitted, however, that our present-day treatment of amenorrhea is far from satisfactory. For permanent cure, my own first love is still low dosage irradiation of the pituitary gland and ovaries, but I will be only too happy to abandon it for the more rational hormone therapy if it be shown to be equally as effective.

The use of progesterone brings up some interesting questions, "Is it substitutive or stimulative?" Dr. Rakoff's studies seem to indicate that, although usually only the former, it can be both, as pregnancy has actually ensued in some cases, in 1 case after low dosage irradiation had failed.

I would like to ask Dr. Rakoff whether he is convinced that progesterone withdrawal bleeding cannot be induced during pregnancy, especially if very large doses are administered?

Several years ago I read a paper before this society on the inadequacy of the treatment of threatened abortion with progesterone. I cited several patients who, threatening to abort, seemed, after a week of rest, sedation, vitamin E, etc., to have quieted down, when a single injection of 10 mg. of progesterone was followed within 24 hours by a miscarriage.

Hamblen made similar observations. Pregnanediol titers were actually decreased by injections of progesterone. The concomitant administration of estrogens and progesterone at times resulted in some increase in pregnanediol. The only definite increases in pregnanediol titers followed the simultaneous administration of chorionic gonadotrophins and estrogen in addition to the progesterone.

In his paper, Dr. Rakoff states that "progesterone in some instances suppresses the release of luteinizing hormone." Could this not in certain cases actually defeat the purpose by inhibiting the patient's own progestin so essential for nidation to continue? In other words, is progesterone completely harmless as a pregnancy test? Dr. Rakoff states that "the failure to bleed arouses suspicion that pregnancy has occurred." Might it not also precipitate bleeding if given in very large doses? My own thought would be to rule out pregnancy first by other means before resorting to large doses of progesterone.

DR. MAHLON HINEBAUGH.—First, we have the observation that, especially in obese women, reduction of fat is followed by the establishment of a somewhat regular menstrual cycle. With these instances of investigation, have you done routine basal metabolic rate studies in order to determine thyroid function in women receiving this progesterone and combined therapy?

DR. RAKOFF (Closing).—Concerning the remarks by Dr. First, I am in agreement that we must be extremely cautious concerning the use of progesterone in the induction of bleeding in patients who might be pregnant. I would hardly advocate the use of progesterone as a routine clinical test for pregnancy at the present time. Thus far in our cases we have never seen high dosage progesterone induce bleeding in pregnancy, and Zondek had the same experience. I do not feel progesterone alone is the best type of medication for a patient who is pregnant and showing evidence of threatened miscarriage. It is very important to add estrogen to this progesterone; it is of course possible that progesterone may inhibit the patient's own endogenous progesterone production. High dosage progesterone has never induced bleeding in the patients who were pregnant. Concerning the mechanism, I think it is puzzling. Our observations answer nothing, but raise many more questions.

Dr. Hinebaugh raised the question of weight reduction and thyroid function with regard to amenorrhea, and I agree that weight reduction is an important part. I would like to add that progesterone is not the answer to all types of amenorrhea treatment. It is simply one approach that can be used. The patients we presented were all thoroughly investigated, and there were none in this group with thyroid deficiencies. None were unusually obese except the group of adrenogenital syndrome; that group was put directly on progesterone therapy and not tried first on weight reduction.

A REVIEW OF THE MATERNAL MORTALITY AT THE CHICAGO LYING-IN HOSPITAL, 1931-1945

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GREAT strides have been made during the past fifteen years in the reduction of maternal deaths in childbirth. The curve is still continuing downward, for the irreducible minimum has not been reached. The great improvement in our special field is the result of many factors. The education of the profession, the education of the lay public, better hospital facilities, and, most important, the dramatic advances that have taken place in the practice of medicine.

Obstetrics has been the beneficiary of all the knowledge in medicine and the basic sciences. The use of blood and plasma, the sulfonamides and penicillin, safer and more efficient methods of pain relief and anesthesia, have all contributed greatly to the dramatic reduction of maternal mortality. However, the extension of our knowledge to the profession and to the public has helped materially to bring these benefits to the patient.

The Chicago Lying-in Hospital admits all women who apply for care without regard as to their ability to pay if their condition warrants specialized care. About 75 per cent of the patients are under the care of a full-time attending staff who are members of the Department of Obstetrics and Gynecology of the University of Chicago. All of these patients are used for teaching, directly or indirectly. The remaining 25 per cent of patients are delivered by a visiting staff, most of the members of which have had special training. The conduct of these patients is subject to review by the attending staff. Consultation during pregnancy and labor is made extremely easy for the patient and her physician, in order to encourage the full use of all the facilities of the institution.

Most of the maternal mortality studies concern themselves with communities at the local, state, or national level. They represent a cross section of obstetric practice in which the general practitioner, the specialist, the small and the large hospitals, all play a role. The teaching institutions have published their statistics, but these have rarely been subjected to the close scrutiny and the cold impartial analysis that all maternal deaths deserve. Generally, it has been recognized that the teaching services, with their carefully trained staffs and their exceptional facilities, have had better results than the rest of the community. However, it has not been sufficiently emphasized that teaching services train young people in the specialty and that there is an increased hazard in the training of a staff. Obstetrics is often emergency medicine, and, in spite of close

*Presented before a meeting of the Chicago Gynecological Society, Feb. 16, 1945.

supervision of the junior staffs, many complications do arise which must be charged to inexperience. The teaching of young physicians is done at a cost which can be kept down to a minimum, but it must be reckoned with.

This report is a careful appraisal of the maternal deaths at the new Chicago Lying-in Hospital, covering a period of thirteen and one-half years. Each death was subjected to a detailed study by the authors, following which all the factors involved were analyzed by the senior members of the staff. The death was considered preventable or not preventable. Preventable factors were always charged to the physician, the institution, or the patient. Although the primary cause of death was determined in each instance, many contributory factors often made the primary cause inevitable. The patient who sustained a rupture of the uterus probably died of hemorrhage within a short time of the trauma, and the death would be accounted for under this primary heading, or she may have survived for some days or even weeks to succumb ultimately of infection. The primary cause of death does not tell the complete story in every case for the contributory factors may make the ultimate outcome inevitable.

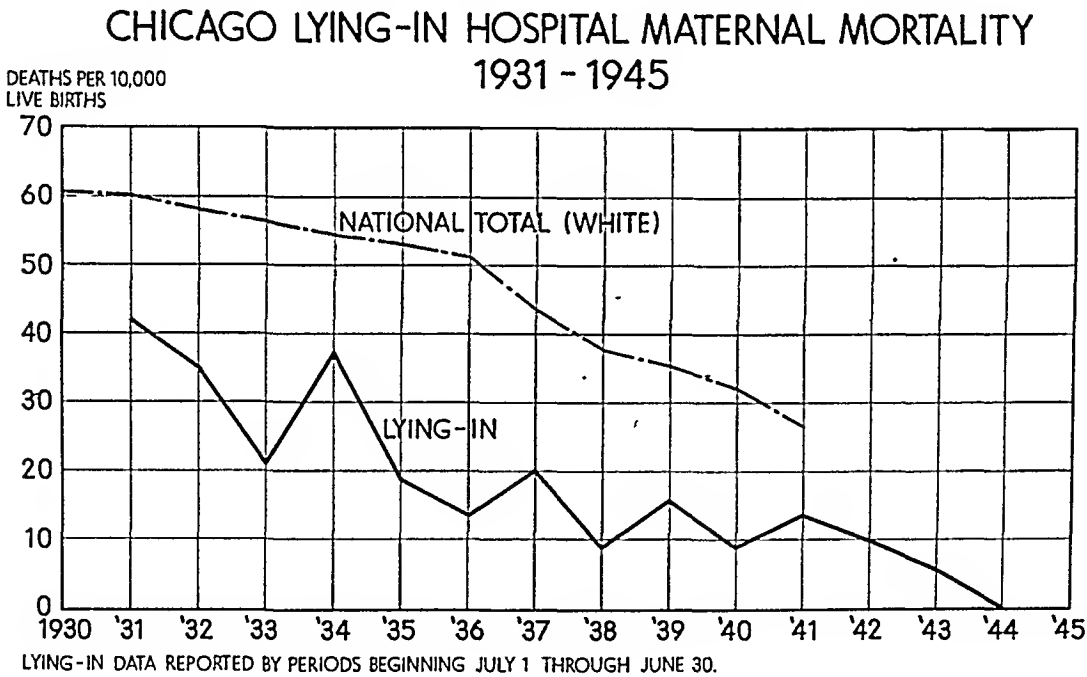


Fig. 1.

Maternal mortality at the Chicago Lying-in Hospital has decreased steadily during the last thirteen and one-half years and the curve parallels the national curve (Fig. 1). The most rapid decline has occurred in the last four years. The improvement of maternal mortality in the last two years may be due partly to the discontinuation of deliveries in the home.

There were 81 deaths in 47,945 obstetric patients, an over-all mortality of 0.17 per cent of all pregnant patients. It is well to point out that Fig. 1 lists the deaths per 10,000 live births so that the figures can be compared with Bureau of Census data.

TABLE I

Deliveries in the hospital	39,719
Deliveries in the home	6,701
Abortions managed in the hospital	1,738
Ectopic pregnancies	132
Total number of pregnant patients	47,945
Total deaths	81 or 0.17%

TABLE II

Delivered and died in the hospital	64
Delivered in the home and died in the hospital	11
Delivered by home service or C.M.C.	9
Delivered by private physicians	2
Delivered and died on home service	3
Delivered in hospital but died at home	2
Sent from home service to Cook County	1
Total number	81
Maternal mortality	0.17%

TABLE III

AGE (YEARS)	
Average age	29.4
Oldest patient	43.0
Youngest patient	19.0
DURATION OF PREGNANCY	
More than 36 weeks	53
From 30 to 36 weeks	11
From 20 to 29 weeks	9
Under 20 weeks	8
Criminal abortion	3
Ectopic gestation	2

Table I shows the distribution of cases in the hospital and in the home as well as abortions and ectopic gestations. All the deaths are included in this report.

In Table II it will be noted that 64 of these patients were delivered and died in the hospital; 11 were delivered in their homes by the Home Service, the Chicago Maternity Center, or a private physician and were sent to the hospital in the postpartum period; 3 women were delivered and died in their homes; 2 women were delivered in the hospital but died at home within the first eight weeks after delivery; one patient was sent to another hospital by the Home Service and died there.

The age of the patients who died may be of some interest. The youngest patient was 19 and the oldest 43 years. The average age of the group was 29.4 years (Table III). Eastman has pointed out recently that youth is a better safeguard against the complications of pregnancy and labor than child spacing. His report once more emphasizes the increased hazards of childbirth late in the reproductive career.

In 53 patients the duration of pregnancy was longer than thirty-six weeks; in 11 from thirty to thirty-six weeks; in 9 from twenty to twenty-nine weeks; and 8 women were less than twenty weeks pregnant when they died (Table III).

Thus, 17 women, or 21 per cent, were less than twenty-nine weeks pregnant. In 3 patients death followed a criminal abortion. Ectopic pregnancy resulted in a fatal outcome in two patients.

The causes of death in the 81 women is portrayed in Fig. 2. In general, our mortality figures follow the general pattern. Infection is the principal cause of death, accounting for 39.5 per cent of the total. This compares with the national figure of 38 per cent for the year 1941. Hemorrhage and shock, however, contribute 16 per cent, whereas the toxemias of pregnancy contribute 7.4 per cent. These compare with 26 and 25 per cent for the country at large (Fig. 3). Heart disease ranks high in our statistics, for it accounts for 16 per cent of the deaths. Autopsies were performed in 77 per cent of the 81 patients who died.

CHICAGO LYING-IN HOSPITAL MATERNAL MORTALITY
1931-1945

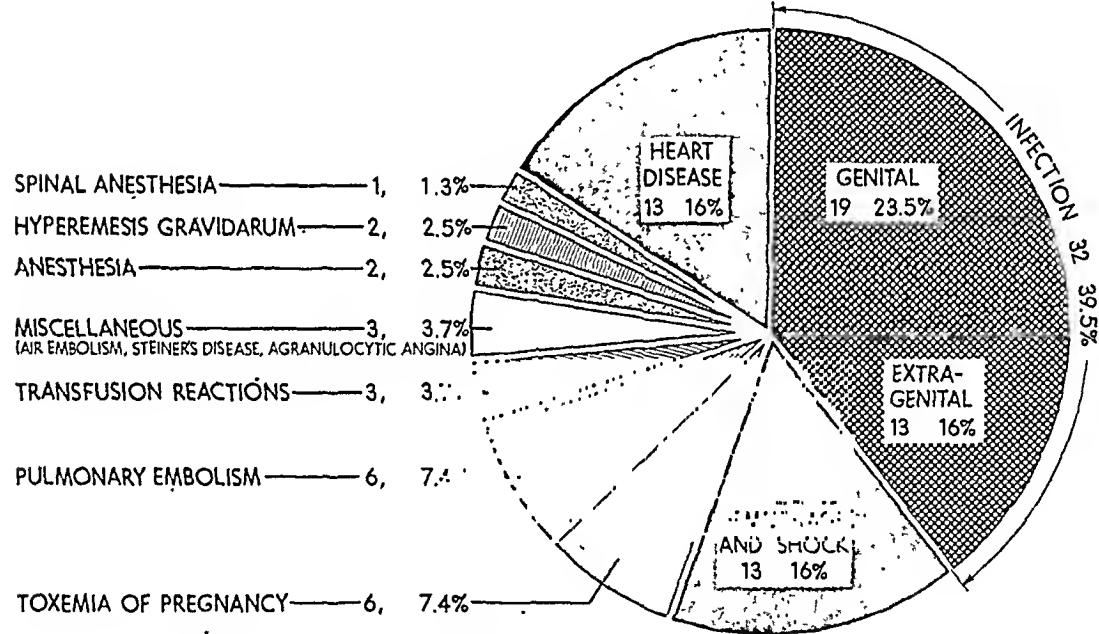


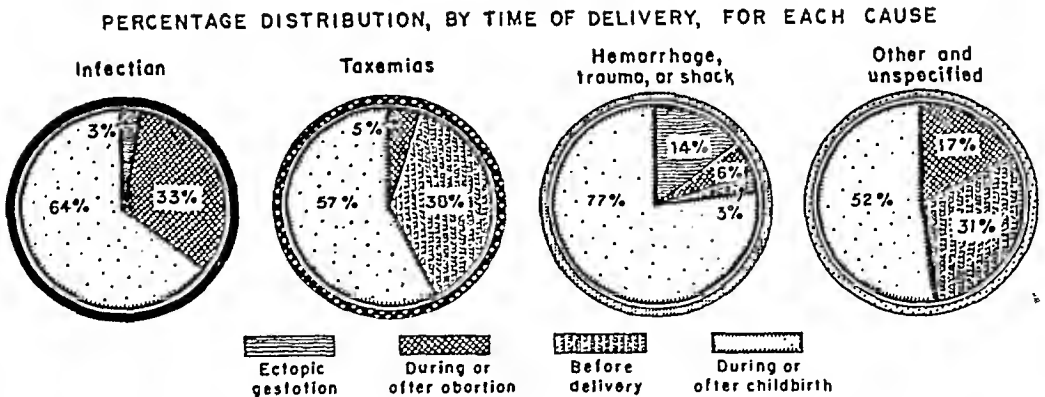
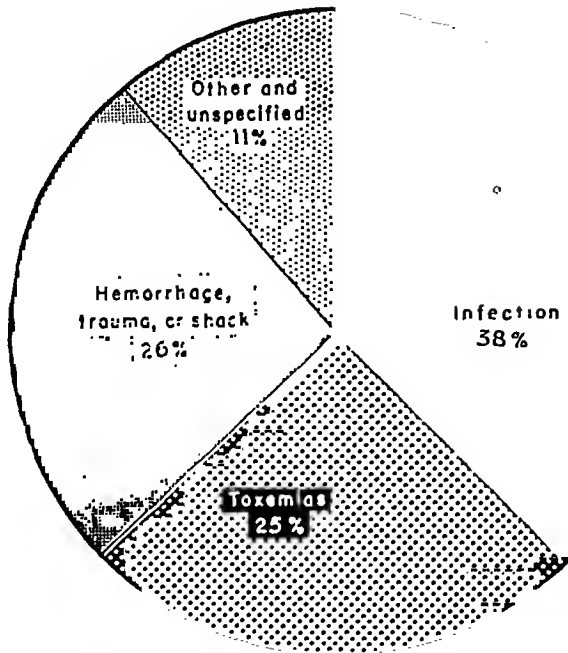
Fig. 2.

A careful analysis of the clinical histories indicates that preventable factors were present in two-thirds of the patients who died (Table IV). In only one patient out of three was the death considered not preventable. Many factors enter into the medical care of an obstetric patient, some of which play vital roles in the ultimate outcome. The patient with serious heart disease who refuses early therapeutic interruption because of her convictions must share in the responsibility of the conduct of so serious a hazard. Unintelligent prenatal care by the physician lulls many a patient into a sense of security that the exigencies

TABLE IV

Total number of deaths	81
Preventable factors present	54—66%
Not preventable	27—33%

of the case do not merit. The lack of proper facilities for the care of the patient or the complicated armamentarium necessary to safeguard delivery must be charged to the institution. Inexperience on the part of the attendant and the failure to recognize omens of danger or the inability to cope with complicated procedures must be laid at the door of the physician. There is an inevitable mortality in obstetrics, but much progress must be made before the irreducible minimum has been reached.



U. S. Department of Labor
CHILDREN'S BUREAU
Chart No. MM 41-4

Based on data from U. S. Bureau of the Census

Fig. 3.—Causes of maternal death in the United States, 1941 (percentage distribution, by cause.)

Infection

A tremendous change is evident in the principal causes of maternal mortality during the last five years. If our statistics are an example of the trend in the large institutions, infection is rapidly disappearing as a major cause of death in obstetrics. This change in maternal mortality, however, is not mani-

TABLE V. INFECTION AS CAUSE OF DEATH

INFECTION			
Genital in origin			19
Extragenital in origin			13
Tuberculosis		4	
Pneumonia		5	
Meningitis (other than Tb.)		2	
Diphtheria		1	
Ruptured appendix		1	
<i>Before July 1, 1939</i>		<i>July 1, 1939, to Jan. 1, 1945</i>	
Deliveries			
Hospital	21,840		17,879
Home	4,606		2,090
Total	26,446		19,969
Genital infections	19		0
ORGANISMS IN GENITAL INFECTIONS			
Hemolytic streptococcus			9
Anaerobic streptococcus			4
Bacillus welchii			2
Other			4

fest as yet in the statistics of the country at large nor in those of the large urban centers. The well-equipped, well-staffed, competently managed maternity has finally become the safest place in which women can have babies.

The disappearance of infection as a major cause of death can be ascribed to a number of factors. First and foremost is the introduction of the sulfonamides and penicillin. Their intelligent therapeutic application has removed the fangs of that ever present specter, infection. These drugs and antibiotics are not applicable to all the virulent organisms involved in puerperal infection, but increasing knowledge will undoubtedly result in new substances effective in an ever-increasing variety of organisms. Preliminary reports concerning the most recent antibiotic, streptomycin, are enthusiastic. More intelligent management of peritonitis has decreased the hazard of this complication. The institution of duodenal drainage by Wangenstein method of constant siphonage and the Miller-Abbott tube has decreased distention and vomiting in peritonitis. Decompression of the distended abdomen decreases the spread of infection, and rest to the intestinal tract promotes localization.

The liberal use of blood, plasma, and parenteral fluids have provided efficient tools for the treatment of infection. The anemic patient is more vulnerable to infection and, once developed, the course is likely to be more virulent than in the patient who has a normal blood picture. Infection is hard on the blood constituents, particularly when the organism is hemolytic in character. Constant blood replacement may be necessary to maintain the body defenses at their optimum efficiency. Lastly, better obstetrics has decreased the hazards of infection. The careful evaluation of cephalopelvic disproportion has decreased the incidence of prolonged labor with its dire consequences. The elimination of the high forceps and the difficult midforceps deliveries has decreased the extent of trauma and resultant infection. The carefully conducted test of labor has increased the safety of cesarean section. Difficult obstetrics has been

made more simple as a result of intelligent approach to the problems of labor and delivery.

Infection is the most frequent cause of death in the present series of cases, accounting for 32 deaths, or 39.5 per cent of all deaths (Table V). The inflammatory process was genital in origin in 19 instances and extragenital in 13. Four of the extragenital deaths were due to tuberculosis and 5 to pneumonia. The streptococcus was the organism involved in 13 of the 19 cases of puerperal infection, and in 4 it was anaerobic in character.

The most interesting observation is that all the deaths from puerperal infection of genital origin occurred prior to July 1, 1939 (Table V). During this period, there were 26,446 deliveries in the hospital and on the home service. Since that date almost 20,000 women were delivered without a single death due to puerperal infection. Thus, it is not too much to hope that the major cause of maternal mortality will ultimately disappear, or its importance become greatly reduced.

Hemorrhage

Deaths from hemorrhage and shock comprise the second most common cause of death in our clinic. In 13 cases it was the primary cause, although it was a contributory cause in many other fatalities (Table VI). Three women who died because they received incompatible blood would have been alive if a transfusion was not indicated. Furthermore, at least 25 of the women who died lost more than 500 c.c. of blood. In 15 instances the blood loss was more than 1,000 c.c., whereas one patient with a ruptured uterus lost 3,300 c.c. Five of the women who lost more than 500 c.c. of blood ultimately died of infection and are charged to this cause. Thus, an excessive loss of blood influenced directly or indirectly the clinical course of almost one-half of these women who lost their lives in childbirth.

Hemorrhage and its resultant shock is a preventable complication in many cases; it is amenable to adequate therapy in most cases. There are many obstetric complications in which hemorrhage plays the dominant role and the man-

TABLE VI. HEMORRHAGE

PATIENT	ETIOLOGY	PREVENTABILITY	AUTOPSY
C.	Abruptio placentae	Yes	Yes
D.	Placenta previa	Yes	Yes
D.	Postpartum hemorrhage	Yes	Yes
S.	Postpartum hemorrhage (Submucous fibroid)	Yes	No
P.	Postpartum hemorrhage (Pre-eclampsia)	Yes	No
S.	Postpartum hemorrhage (Retained placental fragment)	Yes	Yes
S.	Intra-abdominal hemorrhage (Omental)	Yes	Yes
N.	Ruptured ectopic	Yes	Yes
B.	Ruptured uterus	Yes	No
M.	Ruptured uterus	Yes	Yes
L.	Ruptured uterus	Yes	Yes
P.	Ruptured uterus	Yes	No
M.	Ruptured uterus	Yes	Yes

agement includes the proper treatment of the etiological causes. Early in pregnancy, abortion and ectopic gestation are the principal causes of pathologic blood loss. Late in pregnancy, placenta previa and abruptio placentae account for most of the serious hemorrhages. During delivery, trauma and postpartum bleeding associated with the placental stage contribute chiefly to death from excessive bleeding.

In the management of any of these complications, blood loss must never be lost sight of. Ideally, the amount lost must be kept within safe limits, but, when that is not possible, preparations must be made to replace the blood lost. One of the brightest chapters in World War II has been the rapid extension in the use of blood and its constituent fractions. The ease and the simplicity of their administration under the most unfavorable of circumstances must serve as an object lesson for all maternities. Blood and plasma must be readily available at all times and in liberal amounts.

Two of the deaths in this series are charged to placenta previa. During the period covered by the report this diagnosis was made in 271 cases, an incidence of 0.6 per cent of all deliveries. The mortality of placenta previa in our hospital was 0.72 per cent. The two patients who died were treated by cesarean section and, in both instances, their deaths are considered preventable by present standards. The first patient died because of hemorrhage. The extent of the blood loss was not recognized by the attendant who did not have sufficient clinical experience. Preparations for the restoration of the lost blood were delayed and as a result she received too little blood too late to save her life. The second patient entered the hospital because of painless bleeding at about thirty weeks' gestation. A vaginal examination was done and a diagnosis of incomplete placenta previa established. Contrary to the usual practice the delivery was delayed for a week, when a sudden recurrence of bleeding necessitated immediate intervention. A cesarean section was done. Her postpartum course was febrile as a result of pelvic thrombophlebitis. Following several pulmonary infarcts she died on the sixteenth day of massive pulmonary embolism.

The management of placenta previa has become fairly standardized in our institution; although one of the major causes of maternal mortality, proper treatment can reduce this hazard to a minimum. Early recognition of the presence of abnormal placental location is essential. Patients are requested to come into the hospital at the first indication of bleeding. They are typed and matched and blood is made available. The diagnosis of placenta previa is established on pelvic examination. In the event no placental tissue is palpable in the region of the cervical os, the patient is sent home. If the placenta can be palpated covering part or all of the os, a decision is reached as to how best to terminate the pregnancy. Other factors than the degree of previa will influence the choice of treatment.

If the os is partially covered by placenta (incomplete placenta previa) delivery from below is favored. Simple rupture of the membranes may suffice to control the bleeding and to initiate labor. Where this procedure is effective, its simplicity assures the greatest safety from the two hazards of placenta previa, bleeding, and infection. In the event that rupture of the membranes fails to

control bleeding, Willet's method of scalp traction adds no great hazard to the management of placenta previa. Scalp traction properly applied need do no serious damage to the baby. In the patient with a previable fetus, this procedure may prove ideal. The use of Braxton-Hicks' version, as well as the insertion of a bag, have no real place in the modern management of placenta previa. Extensive manipulation through the pathologic lower uterine segment is fraught with too great danger of trauma and its sequelae, hemorrhage and infection. It is interesting to note that 160, or 59 per cent, of all the placenta previa cases at the Chicago Lying-in Hospital during the last thirteen and one-half years were delivered vaginally, and all of the women survived. This result can be charged to the careful selection of patients for this mode of delivery as well as to the meticulous care exercised in their therapy.

Patients with complete placenta previa, the whole os covered over by placental tissue at the time of examination, are best treated by cesarean section. The hazards of delivery through the natural passages far outweigh those of cesarean section. The operation should be carried out when the diagnosis is established. Delay may increase the likelihood of infection. Had this rule been followed, one of the two women with placenta previa who died may have survived. Other factors than the location of the placenta may favor cesarean section as the choice of treatment. Patients who have suffered marked blood loss, the presence of a borderline pelvic contraction, or elderly primiparity may influence the decision for an abdominal delivery in the presence of incomplete placenta previa. In the presence of gross genital infection, abdominal delivery should include hysterectomy, or peritoneal contamination can be avoided by an extraperitoneal operation.

Abruptio placentae was present in 237 patients, an incidence of 0.5 per cent of all our deliveries. Two patients died, a maternal mortality of 0.84 per cent. In both instances the delivery was accomplished vaginally. One of these two deaths was considered preventable.

The mild cases of abruptio placentae can be treated by conservative methods. Rupture of the membranes to hasten the labor, and instrumental delivery of the fetus with an impaired circulation may suffice to save the baby and its mother.

Serious abruptio placentae is a major complication which entails considerable risk for the mother. Most often associated with vascular-renal disease, it probably represents a local obstetric manifestation of this disorder. The patient who goes into active labor after the accident and makes rapid progress because of the tumultuous contractions should be delivered vaginally. However, that this so-called conservatism does not always end uneventfully can be seen in the fact that the two deaths in our series occurred in patients who were delivered from below. The patient who presents a picture of massive hemorrhage, behind the placenta, into the wall of the uterus and retroperitoneally, is better treated by cesarean section. If the uterus fails to contract after emptying its cavity of the dead fetus and the clots, hysterectomy should follow. We have never regretted the decision to remove the uterus because of hemorrhagic extravasation,

but in two instances it was necessary to remove it secondarily, two and six hours after the initial operation. In 71 patients with abruptio placentae, cesarean section was the method of treatment.

The liberal use of blood during labor, delivery, and the puerperium is the most important measure to safeguard the life of the patient. Plasma and parenteral fluids are useful adjuvants, but in the patient who has lost large amounts of blood from the circulation, only whole blood will safeguard her life.

Postpartum hemorrhage as a result of other causes than placenta previa and abruptio placentae accounted for at least four of the thirteen deaths. Excessive blood loss during the third stage of labor was an important factor in at least one-third of the entire series of patients. All four deaths are considered preventable in the light of our present knowledge.

The incidence of postpartum hemorrhage is usually given as 5 or 6 per cent, but modern management of the third stage has resulted in a marked reduction. During the years 1940 to 1943, almost 10,000 women were delivered at the hospital and a diagnosis of postpartum hemorrhage was made in 114, an incidence of 1.1 per cent. Uterine atony in the absence of any other demonstrable cause was present in 36 per cent; trauma in 25.5 per cent; placental fragments in 15.7 per cent; placenta previa and abruptio placentae in 21 per cent; fibroid tumors in 1.8 per cent. These are the usual causes of excessive blood loss and they must be kept in mind in order to approach the therapy logically.

The most common cause of excessive blood loss in the third stage is the mismanagement of this important period. Premature attempts at placental expression before its complete separation results in uterine atony and bleeding. If a natural physiologic third stage is to be awaited, there must be no interference until the placenta has been completely separated following which it can be expressed. However, in hospital practice the placental stage can best be managed artificially by the use of an oxytocic drug. The routine conduct at the Chicago Lying-in Hospital is to administer intravenously 0.2 mg. of ergonovine as the head is being delivered. About thirty to sixty seconds are allowed to elapse before the body is delivered, to give the drug a chance to exhibit its action. Placental separation occurs during the initial contraction of the uterus which follows its emptying. The sudden reduction in the surface area of the placental site results in a rapid clean, and complete separation. The placenta is then expressed promptly. This routine has resulted in a two-thirds reduction in the frequency of postpartum hemorrhage.

Placental fragments remaining attached to the uterus will provoke uterine atony and bleeding. The placenta must be examined most carefully to determine if it is complete and for the possibility of an accessory cotyledon remaining attached to the uterus. If there is any doubt about the placenta, immediate uterine exploration is a safe procedure when carried out under stringent asepsis. Retained placental fragments were responsible for at least two deaths in this series. One of these patients died of hemorrhage shortly after delivery; the other survived long enough to die of puerperal thrombophlebitis and sepsis.

Trauma is a major cause of postpartum bleeding. Careful exploration of the reproductive tract should be instituted whenever the placenta is out of the

uterus and ergonovine intravenously fails to control the bleeding. If the lower genital tract does not reveal the source of the bleeding, the lower uterine segment and corpus must be examined. Rupture of the uterus was present in 7 of the 81 patients in this group. Suture is the only safe way to control traumatic bleeding.

One of the patients who died of hemorrhage immediately after delivery had a submucous fibroid in the wall of the uterus. The usual therapy failed to control the bleeding and hysterectomy was delayed too long to save her life.

Postpartum hemorrhage must be managed in a logical manner rather than by haphazard means. Excessive bleeding prior to placental expulsion cannot be controlled until the placenta is out of the uterus. Credé's expression should be tried, but if it fails, manual removal without too great delay is indicated. A good oxytocic drug administered intravenously (ergonovine or pituitary extract) should now control the bleeding. Further hemorrhage calls for a careful exploration and inspection of the reproductive tract for retained fragments of placenta, trauma, or neoplasms. In the absence of these, an oxytocic drug may now be administered a second time on the assumption that the first did not get into the vein. Uterine tamponade may be indicated, rarely. Hysterectomy is a far safer procedure in the presence of neoplasms or trauma and when uterine tamponade fails to check the hemorrhage. Blood plasma and parenteral fluids are lifesaving if given in sufficient amounts sufficiently early.

Uterine Rupture

Rupture of the uterus may occur in a natural labor which ends spontaneously as a result of tumultuous contractions. It may be induced by a scar in the uterus, the result of a previous cesarean section, or an incomplete rupture in a previous difficult labor which went unrecognized. The danger of uterine rupture following cesarean section is real, although the incidence has been greatly reduced since the advent of the low or cervical cesarean section. It is for this reason that our clinic rarely considers delivery from below after cesarean section justifiable and, with rare exceptions, follows the dictum "once a cesarean always a cesarean." Uterine rupture most often occurs as a result of difficult operative procedures, notoriously version and extraction. This operation, carried out in the patient who has been in labor a long time in a uterus that does not relax completely, carries considerable hazard for the mother as well as for the baby. Lastly, it must not be forgotten that many uterine ruptures in the country at large are the result of the ill-advised use of oxytocic drugs to improve the quality of the uterine contractions, or to hasten delivery when progress is slow. Most authorities feel that the unwarranted use of pituitary extract prior to the delivery of the baby is the most important cause of serious trauma to the reproductive tract.

During the thirteen and one-half years covered by this report there were 30 instances of rupture of the uterus, an incidence of 0.06 per cent. Seven of these women died, resulting in the high mortality of 23.3 per cent (Table VII). A more important consideration is the fact that the deaths in at least four of these seven women could have been prevented by better obstetrics and more energetic management after the accident.

TABLE VII. RUPTURE OF UTERUS

PATIENT	ETIOLOGY	CAUSE OF DEATH	AUTOPSY
B.	Brow presentation; version and extraction	Hemorrhage	No
M.	Pre-eclampsia; bag induction; transverse presentation; version and extraction	Hemorrhage	Yes
S.	Transverse presentation; version and extraction	Sepsis	Yes
P.	Abruptio placentae; Braxton-Hicks' version	Hemorrhage	No
M.	Intrapartum infection; craniotomy and extraction	Hemorrhage	Yes
L.	Pre-eclampsia; medical induction of labor; spontaneous rupture	Hemorrhage	Yes
W.	Spontaneous rupture	Pulmonary embolism	No

In four of these patients the rupture occurred following version and extraction, and in the fifth, during a difficult craniotomy. Although a number of ruptures followed previous cesarean sections, none of these women succumbed. Version and extraction is most often indicated in transverse presentations, deflexed attitudes of the head, and in prolapse of the umbilical cord. Properly carried out, it may be a lifesaving operation for the mother and her baby; poorly managed, it may prove disastrous.

Our fatalities inspire several well-known suggestions to increase the safety of this indicated procedure.

1. Transverse presentations must be recognized early before the rupture of the bag of waters, the impaction of the shoulder, and the development of uterine tetany.

2. Complete dilatation of the cervix must be present before any extraction can be safely carried out.

3. Complete relaxation of the uterus, which can be obtained with drop ether or chloroform only, must be present before any manipulations begin.

4. The early recognition of incomplete and complete rupture will be aided by the prompt exploration of the reproductive tract following difficult deliveries, particularly version and extraction, as well as in all cases of uncontrolled post-partum bleeding.

5. If uterine rupture has occurred, the rapid replacement of blood and plasma in ample amounts, and immediate hysterectomy will improve our mortality.

Heart Disease

Unlike the maternal mortality statistics for the country at large, heart disease shares the second place with hemorrhage as one of the three most important causes of maternal deaths. It was the primary factor in 13 cases, and an important contributory factor in at least four others. Heart disease has now entered the limelight with the time-honored trio—infection, toxemias, and hemorrhage—as a major cause of maternal mortality.

The increase in deaths from cardiac disease may be more apparent than real. The tremendous reduction in maternal mortality involved the more readily preventable causes such as death from infection, hemorrhage, and the toxemias. The incidence of heart disease has not decreased, nor has the maternal

mortality from this complication been reduced, so that it continues as a real hazard in pregnancy. Obviously, any radical improvement must come in the prevention of heart disease rather in its management during the gestation. Nevertheless, the large number of deaths ascribed to this cause must focus our attention on the obstetric management of the cardiac.

The incidence of heart disease in the obstetric services varies from 1 to 4 per cent of all admissions, depending on the locality. In about 95 per cent of these patients it is rheumatic in origin. Pregnancy is a serious hazard to the cardiac because of physiologic changes in the circulation induced by the pregnancy. Stander has demonstrated that the cardiac output begins to rise at the fourth month and increases steadily until near term, reaching an increase of 50 per cent over the normal. It returns to the previous level by the end of the third week postpartum. This increased circulatory load may be sufficient to provoke a break in compensation and its dire effects.

TABLE VIII

CARDIAC DISEASE	
Rheumatic heart disease	10
Mitral stenosis	9
Heart failure—hypertensive disease	1
Auricular fibrillation—cause?	1
Heart failure—acute decompensation	1
PARITY	
Multiparas	9
Primiparas	4
LENGTH OF GESTATION	
24-36 weeks	7
36-38 weeks	2
Term	2
MODE OF DELIVERY	
Spontaneous delivery	7
Outlet forceps	2
Cesarean	2
Undelivered	2

The lesion is important, but may not be the determining factor in the prognosis of cardiac disease in pregnancy. Hamilton believes that mitral stenosis is the most serious pathology. However, the response of the cardiac muscle to the increasing demands is a better guide. In Table VIII it will be noted that in at least 10 of the 13 women who died of heart disease in our study it was of rheumatic origin, and in 9 of these mitral stenosis was the pertinent pathology. Only 2 of the 13 women reached term, and 7 died sometime between their twenty-fourth and thirty-sixth week of their pregnancies. These cases demonstrate the important fact that the serious cardiac patient may succumb any time after the fifth month, and that the delivery, regardless of the mode, may not affect the outcome (two of these patients died undelivered) or may serve only as "the straw that broke the camel's back."

Parity is not an important factor, for nine of these patients were multiparas. The older patient with rheumatic heart disease may have used up her cardiac reserve during the vicissitudes of life. The average length of life in these women

without regard to pregnancy is 40 or 45 years. Thus, a pregnancy in the late thirties may carry a greater risk than in the early reproductive years.

The management of the obstetric patient with heart disease is the most important factor in the ultimate outcome. In 4 of the 13 cardiac deaths, much of the responsibility for the dire outcome rests with the patient. One patient was advised in three different pregnancies that future childbearing was extremely hazardous, and something should be done to make this impossible. Three of the women first reported to the hospital in mid-pregnancy and in marked decompensation. Two of these had symptoms of decompensation for two and five months, respectively.

The physician erred in the conduct of 4 of the patients. In 2 patients a private physician was first aware of the gravity of the complication when they were admitted to the hospital with broken compensation. In 2 other patients who were followed in the outpatient department, the women were allowed to continue their usual activity until serious symptoms developed. Thus, in eight of the 13 cases the intelligent management of the patient by the physician, combined with her cooperation, may have resulted in a far better outcome.

The treatment of obstetric patients with heart disease has been fairly well standardized in our own and other large hospitals. Early diagnoses can be assured by urging patients to consult their physicians early in pregnancy as well as by a careful history (95 per cent have rheumatic heart disease) and complete physical examination. The cardiologist should see the patient to confirm the diagnosis and to evaluate the gravity of the lesion. In our clinic, the consultant follows the patient throughout pregnancy, delivery, and after her return home. It must not be forgotten that the postnatal period with its added physical and mental responsibilities represents a critical period in the life of the handicapped mother. Too often the obstetrician writes the patient off as a successful case when she walks out of the hospital, only to learn that the trials of motherhood are too great for her.

Patients who have been classified as class 1 and 2 cardiacs have no or slight limitation of their normal activity and are seen at frequent intervals during their gestation. They should be hospitalized if they develop fatigue, dyspnea, palpitation, or anginal pain on exertion. One or two weeks prior to term they should be brought into the hospital to await the onset of labor. Delivery can be accomplished by outlet or low forceps in order to spare the heart the additional load imposed upon it by the voluntary efforts associated with the second stage pains.

Class 3 patients have marked limitation of physical activity. Slight exertion will bring on dyspnea, palpitation, or anginal pain. These women should be hospitalized during any illness which may develop, such as an upper respiratory infection. They should be brought into the hospital at the first evidence of decompensation which may be pulmonary congestion. The last month of the pregnancy should be spent in the hospital. Carefully supervised bed rest is still the best cardiac stimulant, although the wisdom of absolute rest in bed has been questioned in the last year because of the increased hazard of thrombosis. The natural onset of labor should be awaited. Ample sedation during the labor

and the elimination of the second stage by low forceps delivery provides the greatest safeguards for the patient.

Class 4 cardiac patients are unable to carry on any physical activity without symptoms. Patients in this class, as well as in class 3, should not have children, for the risk involved is great. If they are seen in the first three months of the pregnancy, therapeutic abortion and sterilization is a justifiable procedure. Beyond this period, they should have long periods of bed rest in a hospital. Digitalis may be indicated for decompensation. If labor should ensue before complete compensation has been restored, delivery from below as described above yields the best results. Cesarean section at an elected time in the last month of the pregnancy should rarely be considered, and then only in the event the patient is thoroughly compensated.

Seven of the 13 patients in this series delivered spontaneously, and 2 were delivered by outlet forceps. Two of the patients died undelivered. Cesarean section on one of the two patients subjected to abdominal delivery was a questionable obstetric procedure and may have contributed to her death. The important lesson to be learned from this small group is that the medical management of the cardiac patient is the most important phase of her obstetric care.

Toxemia

The causes of the toxemias of pregnancy are not known, so that they cannot be prevented. Intelligent prenatal care and the medical management of the noneconvulsive toxemias will prevent the occurrence of eclampsia. This is extremely important, for the mortality of the convulsive toxemias is eighty times as great as the nonconvulsive.

The incidence of the noneconvulsive toxemias during the period covered by the report was 7.4 per cent of all deliveries. During this time 86 patients were treated for eclampsia. Thus the frequency of the latter was 0.018 per cent. The toxemias of pregnancy were directly responsible for 6 deaths, although 23 of the 81 patients who died had symptoms and findings of toxemia. (Table IX).

TABLE IX. TOXEMIA

	INCIDENCE (%)	NO. OF CASES	DEATHS	MORTALITY (%)
Nonconvulsive	7.4	3,435	2	0.058
Convulsive	0.018	86	4	4.6
Primary cause of death			6	
Contributory cause of death			23	

In some of these patients the toxemia contributed greatly to the fatal outcome. The patient who had an induced labor and a difficult delivery may have died of infection. However, it was the toxemia that made obstetric intervention necessary. Four of the six women who died had eclampsia clinically, and the pertinent pathology was demonstrated at the postmortem examination.

Fatalities are largely preventable in the management of the toxemias of pregnancy. The value of intelligent prenatal care is no better emphasized than in this small group of deaths. Five of the six patients had no prenatal care or,

what is equally bad, inadequate prenatal care. The early interruption of pregnancy was advised but refused in one patient. In another woman sterilization had been advised in two pregnancies prior to the one which ended fatally.

The management of the toxemias of pregnancy involves simple rules. Intelligent prenatal care will decrease the hazard of pre-eclampsia. Patients who gain excessively, who develop edema, albuminuria, and hypertension must be treated with the utmost care. Medical management does not cure these toxemias, but it will arrest the process or slow the progress until such time as labor will start spontaneously or it can be started by simple means. If the progress of the disease is not halted and if the patient develops findings as well as symptoms, the termination of the pregnancy becomes imperative. Delivery through the pelvis should be contemplated if at all possible, but if conditions do not warrant the induction of labor because of a long, uneffaced cervix or an inadequate pelvis, abdominal delivery is indicated. The success achieved in the treatment of the toxemias of pregnancy is in no small measure due to the prevention of eclampsia by terminating the gestation in the nonconvulsive state.

The treatment of eclampsia involves the medical management of this toxemia primarily. Adequate sedation, the establishment of good kidney function with the aid of hypertonic glucose solutions, and the induction of labor by the rupture of the membranes will suffice in all but the very serious patients. Delivery from below after the initiation of a good diuresis offers the best results for the patient. Cesarean section is rarely indicated in eclampsia. This major surgical procedure increases the hazards of the convulsive toxemia. Dieckmann states that cesarean section under local anesthesia is justified in "the patient with the severe type of eclampsia with an uneffaced cervix after eight to twelve hours of proper medical care." Following these criteria this operation was performed in 12 of the 86 cases, an incidence of 14 per cent. In some, abdominal delivery was indicated because of cephalopelvic disproportion or the patient developed convulsions after cesarean section for pre-eclampsia.

Cesarean Section

Dieckmann recently presented an exhaustive review of the cesarean sections at the Chicago Lying-in Hospital and a brief résumé will suffice. Eleven of the eighty-one women who died were delivered by the abdominal route. At a superficial glance, it would appear that abdominal delivery comprising 12.3 per cent of the fatalities was a major factor in mortality. A careful perusal of Table X will reveal that in at least three of the cases the operation was performed entirely in the interest of the baby. In three other patients, inexperience of the surgeon was a major factor in the fatality, which can be charged to a teaching service. Two of the women with cardiac disease might have fared better by delivery by the vaginal route, but the gravity of their heart disease demonstrated clinically and at autopsy made any other outcome problematic.

Cesarean section in the hands of the specialist for carefully selected indications in the absence of contraindications need carry no great risk. The modern maternity with its expert personnel, the wide selection of anesthetic agents, carefully suited to each patient, the additional safeguards of the sul-

TABLE X. CESAREAN SECTION DEATHS

PATIENT	INDICATION	LIVED	TYPE OPERATION	CAUSE OF DEATH
1. A	Tuberculous meningitis	11 days	Lap. trach.	(A) Tuberculous meningitis
2. G	Tuberculous meningitis	4 hr.	Classic	Tuberculous meningitis
3. S	Contracted pelvis	25 hr.	Classic	(A) Abdominal hemorrhage
4. A	Myoma	9 days	Classic and myomectomy	(A) Peritonitis
5. D	Placenta previa	3 hr.	Lap. trach.	(A) Exsanguination
6. G	Cardiac disease	11 wk.	Lap. trach.	(A) Peritonitis, acute endocarditis
7. C	Cardiovascular-renal	17 hr.	Classic	(A) Cardiac failure, anemia, chronic nephritis
8. H	Placenta previa	16 days	Lap. trach.	(A) Pulmonary embolism
9. S	Disproportion, diabetes, inertia	10 days	Cesarean hysterectomy	(A) Peritonitis
10. L	Coma, hypertensive encephalopathy	26 hr.	Lap. trach.	Cerebral hemorrhage; eclampsia?
11. H	Pre-eclampsia	29 days	Lap. trach.	(A) Pulmonary embolism

(A): Autopsy.

Lap. trach.: Laparotrachelotomy.

A live baby was delivered in each case.

fonamides and penicillin, and the ready availability of blood and plasma in liberal amounts have helped to remove the unusual hazards of abdominal delivery. The maternal mortality from this operative intervention should truly be the irreducible minimum. Why is it then that Dieckmann reports that cesarean section still carries a mortality of 2 to 5 per cent in the large clinics and perhaps twice that in the country at large? The answer is to be found in the selection of patients for abdominal delivery. The contraindications to the operation are far more important than the indications.

The safest time to do a cesarean is before the patient goes into labor as an elective procedure, or after a carefully conducted test of labor of less than twenty-four hours. Prolonged labor, repeated vaginal examinations, rupture of the membranes longer than twenty-four hours, manipulation, all add to the risk of abdominal delivery. Cesarean section as a way out of difficulty in the patient who fails to make progress after several days of labor and following many examinations, is a hazardous procedure and rarely justified. The criticism that too many cesareans are performed in this country is a valid one, but even greater criticism should be leveled at the fact that too few are done at the right time.

During the period covered by this report, 1,824 cesarean operations were performed at the Chicago Lying-in Hospital. Most of these, 1,704, or 93 per cent, were of the low or cervical type; 98 were Porro cesarean sections; 22 were of the classic type. Cesarean section was the method of delivery in 3.9 per cent of all patients, or less than one in twenty-five. The mortality in all cesareans was 0.6 per cent, but in the low or cervical type, laparotrachelotomy, it was 0.35 per cent.

Anesthesia

Some form of anesthesia is necessary for the majority of hospital deliveries. The anesthetic may play a major role in the conduct of delivery. Anesthesia has become an important medical specialty, and as much care should enter into the

choice and administration of the anesthetic as in the operative procedure. Until the present emergency, all anesthetics were administered by specially trained physicians.

There were two anesthetic deaths in the present series. One woman died during the operation, and the other within twenty-four hours of bronchopneumonia. During this period, over 50,000 anesthetics were administered. Although the mortality was not high, these were preventable deaths. During the same period there were some forty-five instances of aspiration of material into the lungs during an inhalation anesthetic, and eight patients were seriously ill, but recovered. Special measures should be instituted to prevent the aspiration of food and foreign material into the lungs at the time of delivery. Patients in labor should not receive solid food. In spite of this safeguard, a patient is often put to sleep immediately after a hearty meal and serious vomiting results.

All anesthetic agents carry some risk for the mother and the baby. This risk becomes negligible when the anesthetic is carefully chosen and administered by trained personnel. Inhalation anesthetics were most commonly used for vaginal deliveries, and consisted of ethylene or cyclopropane and oxygen, with or without ether. Drop ether was used rarely and chloroform not at all. Local anesthesia is the safest anesthetic agent and is ideal for cesarean section. At least three of every four ceareans were done successfully under local infiltration anesthesia. Recently caudal has been used in a restricted number of cases. No spinal anesthesia was used in obstetrics.

Embolism

Pulmonary embolism as a cause of death is rare, but it accounted for six deaths, an incidence of 0.012 per cent. It will be noted in Table XI that in three of the patients there were no clinical indications of thrombosis prior to the fatal accident, nor were there any evidences of infection during the postpartum period and at autopsy examination. Death followed rapidly after the first clinical manifestations of massive pulmonary embolism.

Infection was the major factor in the causation of the remaining three deaths. Two of the women were subjected to cesarean section and one to hysterectomy following uterine rupture. In all three, pelvic vein thrombosis was

TABLE XI. EMBOLISM

CLINICAL DIAGNOSIS	DELIVERY	POSTPARTUM COURSE	DAY OF DEATH
Normal pregnancy, term	Spontaneous	Normal	1
Normal pregnancy, term	Low forceps; episiotomy	Normal	8
Normal pregnancy, term	Outlet forceps; episiotomy	Normal	10
Severe pre-eclampsia	Laparotrachelotomy	Septic course; pulmonary infarcts	29
Placenta previa	Laparotrachelotomy	Septic; septic pulmonary infarcts	16
Prolonged labor; spontaneous rupture of uterus	Hysterectomy	Septic; stormy; septic pulmonary infarcts; emboli	12

probably induced by infection and was the source of septic emboli to distant foci. These women had warning pulmonary infarcts evidenced by chest pain, pleural effusions, râles, and x-ray findings prior to the fatal massive embolus.

The prevention of uncomplicated pulmonary embolism has been the subject of much clinical investigation recently. Bed rest has been seriously indicted as the most important single cause of embolism. It has been demonstrated that rest in bed favors the development of thrombi in the deep veins of the lower extremities which ultimately may serve as emboli. Some clinicians have urged the elimination of unrestricted bed rest as far as this is compatible with therapy. Patients are allowed out of bed the second or third day after delivery and after major abdominal operations. It is likely that the pendulum has swung too far and that restricted bed rest and moderate activity may offer the greatest aids to recovery as well as the greatest safeguards in the prevention of thrombosis. It has been the policy of the Chicago Lying-in Hospital to refrain from such complete sedation that the patient lies comatose for hours at a time without moving the extremities. Free movement in bed is insisted upon immediately after delivery, and exercises are instituted at an early date. Although normal patients are kept in bed for about eight or nine days, the active puerperal regime prevents stasis of the circulation.

Thrombophlebitis, which is the result of infection, can be prevented by all the measures promulgated for the prevention of infection. The careful selection of patients for cesarean section, care to prevent trauma and infection at the time of delivery, and better obstetries will help to minimize the danger of pelvic vein thrombosis. The patient with placenta previa who died of embolism might have survived if she had the cesarean operation at the time of her first vaginal examination, for virulent organisms may not have been present in the reproductive tract.

The role of antieagulants such as heparin and dicoumarin in the treatment of thrombosis and embolism is still debatable. These drugs properly used may decrease the hazard of embolism in the patient who has had clinical manifestations of infarction or in whom a diagnosis of pelvic thrombophlebitis has been made. Surgical removal of massive pulmonary emboli are dramatic procedures, and few successful cases have been reported.

Transfusion Reactions

The timely administration of blood in adequate amounts is lifesaving, but incompatible blood can be death-dealing. Some of the patients who survive a reaction from the transfusion of incompatible blood sustain permanent renal damage. Three patients in this group of 81 deaths succumbed as a result of a transfusion reaction. In at least one and possibly two of the patients the Rh factor was involved.

Hemorrhage is such an important complication in pregnancy and labor that every patient should be typed as part of the prenatal care. An excessive loss of blood should be anticipated, and proper blood should be made available leisurely, when mistakes are less likely. All obstetric patients should have their Rh

determined, and the Rh- negative women should receive Rh-negative blood. This is particularly important if the patient is to have more than one transfusion, or if she has delivered a baby with evidences of erythroblastosis. The prompt and vigorous treatment of the patient who shows any signs of a transfusion reaction will improve the prognosis.

Conclusions

A summary of the maternal mortality at the new Chicago Lying-in Hospital during the last thirteen and one-half years is presented. The various causes are carefully analyzed and compared with the statistics for the country at large. Preventable factors were present in two of every three deaths. The management of the complications responsible for mortality at the institution are briefly summarized.

Discussion

DR. JAMES E. FITZGERALD.—The commendable results which Dr. Davis presents can be achieved only by the concerted effort of the staff of a well-organized hospital. For comparison let me tell you what happens in a charity hospital in which the patients are not selected or are not under the control of the members of the staff, such as the Cook County Hospital.

We delivered 45,557 patients with a total mortality of 0.31 per cent, which is almost twice as high as the percentage Dr. Davis presents. Those deaths are accounted for by the fact that many patients are admitted to a charity hospital with no prenatal care and frequently with inadequate care at delivery elsewhere. We accept responsibility for all deaths that occur in the hospital. Still, I think that our series compares favorably with his series, and we have much less supervision of the members of our active staff, who are usually residents and interns, than he has of his personnel at the Lying-in Hospital. I should like to comment on the statements made by Dr. Davis, that some improvement in the mortality during the last two years may be due to discontinuance of deliveries at home. This would be definite news to the founder of the institution and its biography in the public press. He says that only three women delivered at home in fifteen years died, so discontinuing the home service for two years had very little effect on the Lying-in maternal mortality.

In Dr. Davis' series he has as many deaths from heart disease as from toxemia. In the Cook County Hospital we have had only two deaths from heart disease in pregnancy during seventeen years in patients over whom we had complete control, and who went to our cardiac clinic for prenatal care. On the other hand, Dr. Davis finds that since the administration of the sulfonamides and penicillin the mortality from infection has decreased. At the Cook County Hospital the mortality from infection has not decreased since the advent of the sulfonamides and penicillin.

One other question that Dr. Davis brings up is the management of placenta previa, and he states that he is accustomed to make a diagnosis of placenta previa by pelvic examination. It has been increasingly our opinion in a large series of cases that we did as much harm in attempting to make a diagnosis of placenta previa by pelvic examination as we did when no diagnosis was made.

DR. JAMES A. GOUGH.—During the last five years at St. Luke's Hospital we have confined 6,000 women, or, approximately, 100 per month. In those 6,000 women there were 10 maternal deaths. During this same interval 267 abortions were cared for in our hospital and 43 ectopic pregnancies. There were no deaths from the ectopics. There was one death from a septic abortion, the patient admitted in coma and dying a few hours later.

Practically 60 per cent of our patients are private and 40 per cent are confined by the resident staff, and the mortality is distributed exactly in that proportion, six deaths among

the private patients and four in the dispensary service. Of these deaths, postmortem examinations were obtained on six, and in the four which were not posted the causes of death were sufficiently obvious to be unquestioned. The causes of death were as follows:

Pulmonary embolism	2
Atelectasis during cesarean section	1
Cardiac disease	1
Eclampsia	1
General peritonitis following cesarean section	1
Empyema	1
Pneumonia	1
Massive intracranial hemorrhage from rupture of the basal artery	1
Postpartum hemorrhage	1

Our incidence of maternal deaths is thus comparable to the series which Dr. Davis has reported, but we have taken advantage of the time element, and our report is based on the last five years only, while Dr. Davis' is based on thirteen years or more.

DR. LUELLA E. NADELHOFFER.—I thought you might be interested in a comparable period for the whole city of Chicago. Here, in 1944, in 60-odd hospitals there were 59,379 live births. Our mortality in Chicago has declined in the last thirteen or fourteen years. In 1931, the year in which Dr. Davis started, the mortality rate for Chicago was 46 per 10,000 live births, and for the United States as a whole 66 per 10,000 live births. In 1944 our provisional maternal mortality in Chicago was 16 per 10,000 live births, which is the lowest it has ever been. The latest we have for the United States was in 1942, when it was 25 per 10,000 live births.

It is difficult, as Dr. Gough said, to state comparable statistics over this long period of time, but the last year for which we analyzed the causes of death was in 1943, in which we had 128 maternal deaths. The chief causes were 20 from abortions, most of which were septic; 5 from ectopic pregnancy; 25 from hemorrhage; 30 from toxemia; 22 from infections, and 20 from other causes. The essential difference between these statistics and the ones presented by Dr. Davis is that he has no deaths from abortions. We still have many septic abortions which are admitted to other hospitals. There are more deaths from cesarean section in the city as a whole. The last time I went over the figures about one-fourth of the deaths followed cesarean section. There are more eclampsia deaths than in his series. I agree with Dr. Fitzgerald that septicemia is still a leading cause of death in Chicago. We included abortions with that.

In the Bulletin from the Metropolitan Life Insurance Company in August, 1944, it was stated that a large number of maternal deaths are preventable. Septicemia is still the greatest cause in their series of 2,800 deaths. The Sub-Committee on Maternal Mortality of the Joint Maternal Welfare Committee of Cook County, of which Dr. Baer is Chairman, feels that one of the chief aims should be against abortion deaths. We do not know just what can be done about these. It is largely a local problem. The medical profession should perhaps lead the way in trying to find a means of preventing these deaths from septic abortion.

We feel in Chicago that timely and adequate consultation is a factor in the prevention of some of these maternal deaths, especially in the smaller hospitals.

In Dr. Davis' statistics, there were a number of cases in which hemorrhage was mentioned. I believe that is one of the most important causes of maternal deaths before our Sub-Committee on Maternal Mortality. Again and again the Committee says that adequate blood replacement was not given. In a hospital staff meeting which I attended on Wednesday, it was suggested, that in cases of placenta previa, not only one flask of blood should be given but two, three, or four. That is possible in a hospital where there is a blood bank, but in the majority of smaller hospitals it is not possible to have this blood available. We believe that some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. The Joint Maternal Welfare Committee has been working with some outstanding hematologists in the city and they are planning to institute a program whereby plasma and resuspended red blood cells will be available in the city of Chicago.

DR. EDWARD ALLEN.—Are we justified in our teaching of obstetrics in talking about the irreducible minimum? When we compare the results of the private service, the house clinic service, and the outpatient service, we find a marked difference both in the mortality and the morbidity rate. The operative incidence on the house teaching service is about ten times as great as that of the outpatient service. I realize fully that we must teach some operative obstetrics to students, but perhaps our teaching would get better results if our house operative incidence were more nearly that of the outpatient service.

The prime interest of the obstetric patient is safety to herself and baby, and secondarily, the relief of pain. I believe a warning should be sounded in the teaching of students concerning the increased mortality and morbidity which perhaps may result from the obstetrician's attempts to relieve all pain during childbirth.

DR. H. W. SHUTTER.—In Milwaukee we opened the Milwaukee Hospital and proceeded to get fine statistics. We delivered 4,300 women without a death, and then we had 4 deaths in the next 800 deliveries.

We have had some enthusiastic users of caudal anesthesia, and we have had two deaths. The second one died in thirty minutes from the time injection was started. Since then we have cut down caudal anesthesia to cases where it is really indicated.

DR. EUGENE A. EDWARDS.—The highest incidence of death is due to infections following abortion. I would like to see cooperation between the City Health Department, the State, and the medical profession to reduce the incidence of abortion. The highest incidence of infection follows abortion. I believe this can be reduced. I would like to see cooperation between the State Health Departments, and the medical profession in punishing the abortionist.

DR. DAVIS (Closing).—The only question that I wish to answer is the one raised by Dr. Allen. We are all agreed that the safest way for the normal woman to have her baby is to deliver as naturally as possible. If all pregnant women were carefully screened and those with complications were confined in a well-conducted maternity, the others could be delivered at home safely. However, women prefer to be delivered in hospitals. They demand the benefits of analgesia and anesthesia. These refinements of obstetrics necessarily increase the incidence of operative deliveries and the complications of the third stage. Everything possible must be done to safeguard obstetrics in our hospitals, for these institutions are the logical places for women during childbirth.

Home delivery services are slowly disappearing, and it will not be long before most of the women will be confined in hospitals. In the urban centers few births occur in the homes. In the country at large, there has been an increase of 27 per cent in the hospital births in the last five years. During the last year almost 70 per cent of all babies born in the United States were delivered in hospitals. Our present task is to promote greater safeguards for hospital deliveries so that every patient can be delivered safely in a hospital by a competent physician.

THE EVOLUTION OF THE BIOLOGIC CONCEPT OF THE ETIOLOGY OF LATE TOXEMIA

J. HOFBAUER, M.D., CINCINNATI, OHIO

THE Renaissance of obstetrics and its elevation from an almost exclusive interest in mechanical aspects to the rank of a science is primarily due to a succession of constructive advances made in this century along the avenues of biologic investigation. They paved the way for a realistic coordinated approach to the intricate problem of toxemia and played a telling part in providing a reasonable explanation for its basic mechanism. In contrast with the melancholy iteration in the course of discussions upon the etiology of the late toxemia to the effect that most of the stream of research effort has been losing itself in the sand, recent orientation takes the position that the answer no longer eludes us.

Ideas seldom spring full-fledged from the mind of man. It will be profitable to trace the excursions made in planned biologic researches into hitherto untrodden fields. The integration of an array of newly acquired fundamental facts into a coherently unified concept of toxemia, although sharply at variance with the traditional trend of thought, marks the harvest of investigations spanning the range of four decades in this sphere. The detailed study of the histology and function of the chorionic villi of the human placenta revealed among other hitherto unknown features the occurrence at any stage of gestation of syncytial buds which project into the surrounding maternal blood spaces, gradually detach themselves and finally dissolve in the maternal blood stream. The remarkable vital activity of these syncytial derivatives was discernible in specifically stained microscopic specimens. Experimental evidence shows that these fragments act as a powerful formative stimulus to various maternal ductless glands which respond with hyperplastic changes. The chromophobe hyperplasia known to occur during pregnancy in the anterior pituitary gland was obtained by various investigators with the administration to experimental animals of estrogens (Berblinger, Vasquez-Lopez). However, the disintegration of these syncytial elements represents an important source of protein split products, histamine-like substances. The biologic significance of this event becomes immediately apparent if it is remembered that the shedding of syncytial buds occurs from a chorionic surface which at term measures 6.5 square meters. Foremost among the maternal organs involved in the damage sustained by the abundance in the blood of such protein split products is the liver which both by specific function tests and in microchemical stains revealed glycogen deficiency as the principal biologic deviation. In my original communication (*Arch. f. Gynaek.*, 1909) as well as in a more extended discussion (*Am. J. Obst. & Gynec.* 26: 311, 1933) the bearing of this phenomenon on certain derangements of metabolism during gestation was detailed. There are quoted interesting and informative facts concerning hepatic lability during the second half of normal gestation in forty out of a hundred apparently normal cases and definite in-

sufficiency of liver function in toxemia. Of more recent date is the recognition of the significance of the syncytial fragments as implements of conveyance into the maternal circulation of certain hormonal and chemical substances which are normally stored in large quantities within the human placenta (sex hormones, acetylcholine). The selective action of the chorionic epithelium in the assimilation and placental transmission of the requisite material for fetal nutrition was fully detailed in my monograph *Biology of the Human Placenta* (1905), and has since received universal recognition, while the view which tended to relegate to the placenta the function of merely a semipermeable membrane is losing favor.

The introduction of posterior pituitary extract in 1911 for the initiation of rhythmic uterine contractions in the first and second stages of labor and for the induction of labor aroused interest in other pharmacologic properties of the preparation. In consequence, clinical observations and experimental premises joined in favoring the view of a posterior hypophyseal-cortico adrenal mechanism underlying late toxemia (Zentralbl. f. Gynäk., 1918). The announcement stimulated a prodigious amount of work and debate as summarized in a paper "Recent Advances in the Study of the Etiology of Eclampsia." Proceeding from the remarkable identity of the chemical findings in the blood of eclamptics and of laboratory animals which had received intravenously postpituitary extracts, the accumulated pertinent experimental and microscopic data obtained by various investigators concerning the nature of late toxemia were collated. The concept of an undue pitressin effect as the basic factor involved was advanced (AM. J. OBST. & GYNEC. 26: 311, 1933).

The result of extensive experimental studies concerned with the intravenous administration of *histamine* to pregnant and nonpregnant animals (carnivora) served to contribute to the understanding of the etiology of the toxic type of premature separation of the normally implanted placenta (AM. J. OBST. & GYNEC. 12: 159, 1926). Recent significant data tend to elineh the argument that the condition virtually represents a histamine effect. In the wake of the discovery of histaminase in the human placenta (Danforth, D. N.: Am. J. Physiol. 119: 294, 1937) Mareou, Effkemann, Stern, Werk, Zeller, and Ahlmark reported that during normal gestation the blood invariably shows an extraordinarily high activity in destroying histamine. This phenomenon is specific and does not occur in any other condition. The activity of histaminase was found diminished in severe pre-eclampsia and particularly low in premature separation of the placenta. As a corollary, the blood level of histamine and histamine-like substances in the latter condition appeared fifty times higher than normal (L. Cusmano, Ginecologia 7: 285, 1941, rev. in Chem. Abstracts, 1945, p. 3353). The inference concerning the true nature of the condition under consideration seems inescapable. In consequence, the administration of adrenal cortex preparations which are known to antagonize histamine, and of blood transfusions, as well as the abandonment of ether anesthesia in the treatment of the toxic type of premature separation of the placenta, as suggested in the communication mentioned above have proved their therapeutic value.

Coordination of data concerning certain well-defined pharmacologic principles represents an integral part of the recently advanced reorientation on the etiology of late toxemia (West. J. Surg. 49: 615, 1941; Cincinnati J. Med. 23: 107, 1942; Am. J. Surg. 45: 361, 1944). While in the past the placenta was generally considered the chief characteristic of the pregnant state and, in toxemia, the principal factor responsible for the elaboration of "toxins," the new tenet inclines to the view that the pregnant state is essentially conditioned by the altered basic endocrine pattern. Notable among the hyperplastic changes occurring in the ductless glands during pregnancy are the phenomena in the adrenal cortex, the thyroid and the anterior hypophysis. In the present discussions the demonstration of increased secretion of the basophiles during the last trimester of normal gestation and of cortical structures had first call in view of clinical evidence obtained in recent years that the adrenal cortex as well as the pituitary basophiles may have pressure potentialities (G. A. Perera, J. A. M. A. 129: 537, 1945). These facts, in conjunction with augmented reactivity of the arterioles to pitressin as the result of the presence during pregnancy in the blood of placental sex hormones in concentrations far above anything occurring in the nonpregnant state, served as the basis for the appreciation of a delicately adjusted equilibrium during normal gestation between the opposing tendencies on the blood pressure of certain endocrine factors and placental acetylcholine. A disturbance of this balance in toxemia was demonstrated by our report of remarkably low acetylcholine values in 28 placentas and by the unequivocal evidence adduced by Mukherjee of increased concentration in the blood of postpituitary principles in toxemia (J. Obst. & Gynae. Brit. Emp. 48: 586, 1941). In addition, as quoted in my papers, cholinesterase activity in the toxemic placenta was found to be significantly higher than in normal conditions. This fact was recently fully confirmed by the studies of Woodbury (J. A. M. A. 128: 585, 1945). Exposition of functional aberrations of the placental enzyme systems, implied here and recorded above relative to the discussion on histaminase, attains significance in the light of recent work which tends to illustrate the influence of the hormones of the adrenal cortex, the pituitary, and the thyroid on the enzymic activities of various organs. The presence in the toxemic placenta of widespread areas of disintegration, occasionally only discernible on microscopic study (J. Young), has been generally accepted as an item of important information. The interrelation of these acute placental lesions to the occurrence of increased cholinesterase with rapid destruction of placental acetylcholine is apparent. Experimental evidence adduced by Hartmann demonstrating that prolonged spasm of the umbilical vessels may be elicited by histamine or by postpituitary pressure principles (1930) serves to throw light on the mode of formation of the red infarcts in the toxemic placenta, while the view that toxemia is produced by the absorption of protein split products from the infarcted area (tyramine, guanidine) is not supported by any evidence.

To the previously noted facts along clinical, experimental, morphologic, and chemical avenues quoted in favor of the concept of undue effects of the pituitary pressor principle as the unifying factor in the analysis of the man-

ifestations of late toxemia has recently been added the demonstration by Stehle and Bourne of the blood concentrating effect and of the phosphorus raising action of the pressor hormone (J. Physiol. 64: 229, 1943) in gratifying accord with factual data in toxemia. Such evidence is eloquent. There is indeed reason to regard the analogy complete when it is recalled that anoxia of the tissues as a fundamental aspect of toxemia also occurs consequent upon the intravenous administration to unanesthetized dogs of pitressin (Grollman, Geiling).

Critical analysis of the objections raised by L. Dexter and his associates to the significance of pitressin as an etiological factor revealed that they are unsubstantiated (J. A. M. A. 122: 892, 1943). Indeed, the recent investigations of Sawyer and Ettinger conclusively demonstrated in dogs the blood pressure raising property of posterior pituitary extracts in conformity with former observations recorded by Leimdoerfer, Keith, and Griffith (Canad. J. Research 22: 26, 1944). In this discourse, it is worthy of note that quite recently another link has been added to the chain of evidence pointing to the fundamental part played by the pituitary in the disorder under consideration. Conglomeration in the anterior pituitary lobe of basophiles in discrete foci in eclampsics, as first described by Berblinger, has been recently observed in the large majority of cases studied by other investigators. These findings may have a bearing on the occurrence of a high gonadotropic content of the serum in toxemia. In the light of recent evidence which indicates a distinct relation of the basophiles to hypertension and to hyperplastic changes in the adrenal cortex, these observations may be significant.

Dieckmann and Michel (1937), and Schockaert and Lambillon (1937), working independently, showed that pre-eclampsia is characterized by a marked degree of hypersensitivity to injected vasopressin. With normal gestation exhibiting a state of refractoriness to vasopressin, it seemed necessary to postulate an inhibitory factor which under normal conditions holds the sensitizing effect of estrin on the arteries in check and is lacking in toxemia. Kustner, Obata, Byrom, DeValera, and Keller likewise predicated an inhibitory agent in normal gestation. Investigators who recently reported that hypertensive pregnant animals commonly develop a well-marked decline in blood pressure during the last part of pregnancy believe that this phenomenon occurs because the placenta forms some antipressor substance. Being a powerful vasodilator acetylcholine, significantly constant both as to presence and remarkable concentration in the normal placenta suggests itself as the substance provided by Nature for the neutralization of the effects on the hyperreactive arteriolar tree of vasopressin and of certain overactive hormonal products (adrenal cortex, thyroid). The recent experimental demonstration of an antagonistic pharmacodynamic action on the vasomotor mechanism of the pituitary pressor principle and acetylcholine (1941) bears on the existence during normal gestation of a delicately balanced blood pressure regulating mechanism. Dislocation of this equilibrium in toxemia as the result of impaired destruction of pitressin in the functionally deficient liver and choline deficiency in the placenta and the blood, with the resulting inadequately opposed effects of naturally secreted postpituitary pressor principles, may be regarded as the keystone to the interpretation of the diverse manifestations of

late toxemia, a morbid degree of generalized vascular spasm, tissue anoxemia, and derangement of water and carbohydrate metabolism constituting the essential sequela. In our concept, to the placenta is accorded merely the role of the determining factor in initiating and sustaining the increased activity of the adrenal cortex, the thyroid, and pituitary gland.

The present view broadens into a larger conception of the complex mechanism concerned in the causation of late toxemia. If examined with an open mind and discriminating balance, it requires no special prophecy to recognize that we stand at the threshold of the conquest of the disorder. The burden of proof must be with those in disagreement to the views advanced.

Disease, if it is to be understood, must be interpreted in physiologic terms, while rational therapy depends upon the basic comprehension of the cause of the disorder in question. In previous communications on the subject, among the cardinal aspects which enter into the therapy of toxemia the preservation as far as possible of the functional integrity of the liver as the organ most concerned with the control of the endocrine secretions of pitressin and thyroxine and of glycogen was stressed. To this end, in addition to the proper diet, the administration in the prenatal period of an adequate supply of vitamins B and C and of calcium, which exercises a protective power in relation to the liver, was suggested.

As indicated in a previous paper, sedatives (morphine, barbiturates, magnesium sulfate) exert a controlling influence over the effects of postpituitary principles on the midbrain. The significance of these facts is evident in the light of the demonstration by Verney, Danilov, Chang, and Lim, that painful stimuli of the splanchnic nerves cause an increase in the output of the hormones of both the posterior pituitary and the adrenal cortex.

A PARAVESICAL EXTRAPERITONEAL CESAREAN SECTION TECHNIQUE

With an Analysis of 160 Paravesical Extraperitoneal Cesarean Sections

JAMES FRANCIS NORTON, M.D., JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

THAT there still occurs, especially in the larger obstetric services, problems which can best be managed by recourse to an extraperitoneal cesarean section is a fact more or less generally conceded. All too frequently one finds a patient long in labor, with a live baby, presenting part unengaged, or only fixed at the inlet, membranes ruptured for many hours, and perhaps frankly or at least potentially infected, and in whom delivery through the birth canal with a satisfactory result for both mother and child is not to be expected. These patients truly present a serious problem for adequate and satisfactory obstetric management.

In managing this type of problem, we feel that the best results may be obtained by utilizing an extraperitoneal approach to the lower uterine segment and thus effecting delivery by cesarean section without invading the peritoneal cavity.

The more widespread use of extraperitoneal cesarean section has been retarded by one or more of a variety of objections raised against the operation. Most frequently heard are: (1) the technical difficulties encountered in the performance of the operation; (2) the need for far more than ordinary operative skill for its adequate performance; (3) the relative infrequency with which one finds a true need for the operation; (4) the possibility of opening the peritoneum and thus defeating the purpose of the operation; and (5) danger of injury to either or both the ureter and the bladder.

We are presenting here a paravesical extraperitoneal cesarean section technique which in our hands has served well; the various steps of the operation are deemed to be not too difficult technically. It does not demand a degree of surgical competency over and beyond that possessed by the average obstetric surgeon; and its various steps can be mastered with an occasional ease, and the relative infrequency with which one is called upon to utilize the procedure need offer no serious objection to its use.

We are analyzing 160 paravesical extraperitoneal cesarean section techniques performed at the Margaret Hague Maternity Hospital with particular reference to objections (4) and (5), and offer in addition an operative technique which we think obviates the other objections set forth above.

The first extraperitoneal cesarean section at the Margaret Hague Maternity Hospital was done Dec. 26, 1931, by Dr. Samuel A. Cosgrove. The technique as originally set forth by Latzko was followed. In August of 1932, Burns¹

operated on the fourth case at the hospital and demonstrated the technique described by him of utilizing a paravesical approach to the lower uterine segment. In the group of cases here analyzed, the only one constant technical factor is the paravesical approach to the lower uterine segment. The technique here presented is the result of many modifications, deviations, and evolutions from various points in the techniques already set forth. Simply stated, it is a paravesical approach to the retrovesical area of the lower uterine segment and an enlargement of this area to obtain adequate exposure for delivery of the baby, all the time remaining infraperitoneal (i.e., below the posterior fold of peritoneum). Nothing of an original nature is claimed for the methods described in this presentation. It represents what we consider to be improvements in the already described techniques, which improvements stem from a clearer and more definite knowledge of the anatomy of the various layers of the pelvic fascia and the duplications and reflections of the pelvic peritoneum, together with an excellent opportunity to test many variations from the already described and established procedures until we obtained what we consider to be a technique which has proved to be simple, adequate, and satisfactory. Multiple variations and improvements from the procedure here set forth fall well within the scope of any competent surgeon.

For the adequate understanding of an extraperitoneal approach to the lower uterine segment, accurate knowledge of the anatomy of the pelvic fascia and the relationship and reflections of the various layers of peritoneum is of primary importance. We do not feel that it falls within the scope of this paper to detail the anatomy. It is better said elsewhere.²

While the operation when properly performed is de facto truly an extraperitoneal undertaking, it seems to us that the rationale and anatomic basis of the entire procedure may be better understood and its technical performance more easily mastered if the two main steps so necessary for its proper completion were more emphasized, viz., a retrovesical infraperitoneal exposure of the lower uterine segment. These two concepts of retrovesical and infraperitoneal constitute the basis for the proper management of the entire operation.

The procedure here developed concerns itself with three distinct steps:

1. Paravesical approach to the retrovesical area of the lower uterine segment.
2. Identification of the infraperitoneal portion of this retrovesical area of the lower uterine segment.
3. The infraperitoneal enlargement of this area.

Technique

General preparation.—Anesthesia as elected: usually 100 mg. spinal novocain. (1) Vaginal preparation and examination. (2) Insertion of retention catheter into bladder. Two hundred cubic centimeters of colored solution run in and tested for ease of flow out. Use 1.6 per cent indigo carmine (one 5 c.c. ampule of 0.8 per cent/1000 c.c. distilled water). (3) Abdominal preparation.

I. Approach to the Retrovesical Area of Lower Uterine Segment

(4) Left paramedian incision through skin from above distended bladder, down to symphysis: expose and incise anterior sheath of left rectus. (5) Rectus muscle is separated

by blunt dissection from the underlying transversalis fascia, and then lifted upward and retracted laterally. (6) Visualize large vessel (deep epigastric) which runs parallel to the rectus. (7) Identify at upper part of left lateral surface of bladder (the left paravesical space) an area of chicken yellow fatty tissue (Fig. 1). (8) Insinuate index and second finger into the left paravesical space in region of the chicken yellow fat and lift from the underlying bladder the transversalis fascia and the anterior sheath of perivesical fascia. Incise these layers of fascias and extend the incision well over beyond the midline of bladder. This incision of fascia should be directed downward in order to avoid injury to the anterior peritoneal fold at top of bladder. These two layers of fascia may come off singly or in layers—if singly, repeat procedure until bladder muscle is exposed (Fig. 2). (9) Partially empty bladder. (10) Return to the left lateral surface of the bladder and with finger dissection started in the left paravesical space along the left surface of the bladder, begin removing the bladder from the underlying lower uterine segment.

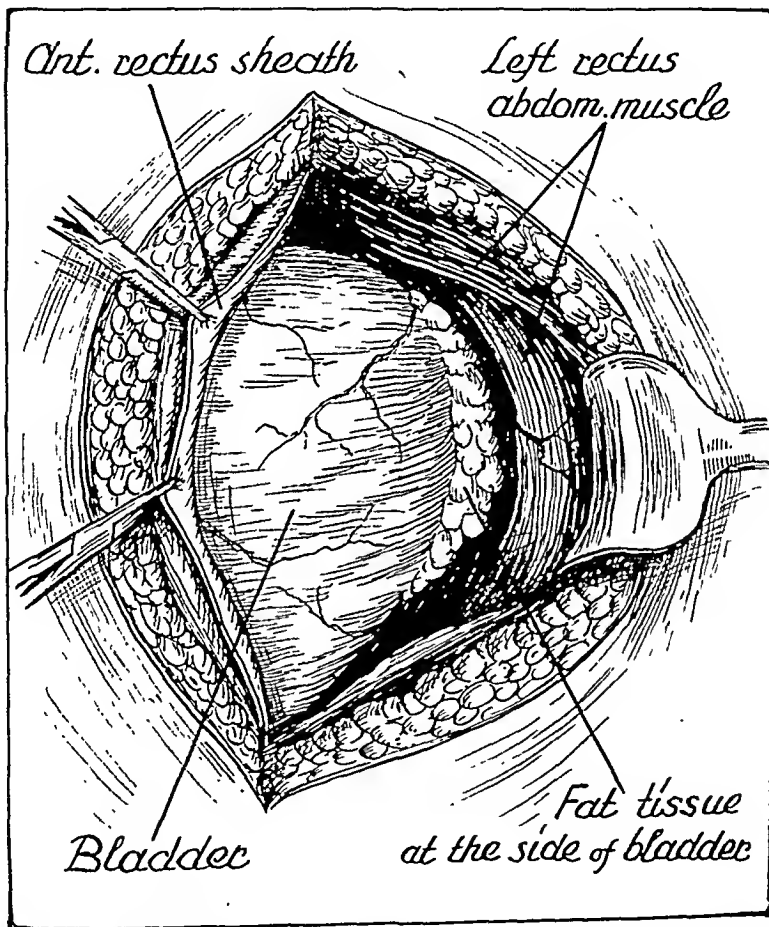


Fig. 1.—Area of "chicken yellow" fat tissue at the side of distended bladder; the left rectus abdominus muscle must be retracted upward and laterally for proper exposure of this area.

II. Identification of Exposed Retrovesical Infraperitoneal Area of the Lower Uterine Segment

(11) After the bladder is but partially removed there will be exposed a triangular area on the anterior surface of the lower uterine segment. The upper border of this triangle is formed by the posterior peritoneal fold; the lower mesial border by the partially removed bladder; the lateral border by the parietes (Fig. 3).

III. The Infraperitoneal Enlargement of the Retrovesical Area

(12) Incise the fascia in this bared triangular space. This is the posterior sheath of the paravesical fascia and the anterior sheath of the periuterine fascia. (13) With Richardson retractor, retract the posterior peritoneal fold upward, the bladder downward to the right, and the fascia laterally to the left. This retraction of posterior peritoneal fold upward and the bladder downward by the means described is as easily accomplished as when one is performing a transperitoneal lower segment operation and prepares two flaps of peritoneum over the lower uterine segment. The lower flap with the bladder is easily pushed off the uterus from above downward, and the upper flap of visceral peritoneum over the uterus is just as easily separated and is pushed upward. (14) If room is deemed insufficient (and this has been but seldom) then (15) pick up the upper flap made by procedure No. 8 (this flap consists of both the transversalis fascia and the anterior sheath of the perivesical fascia)

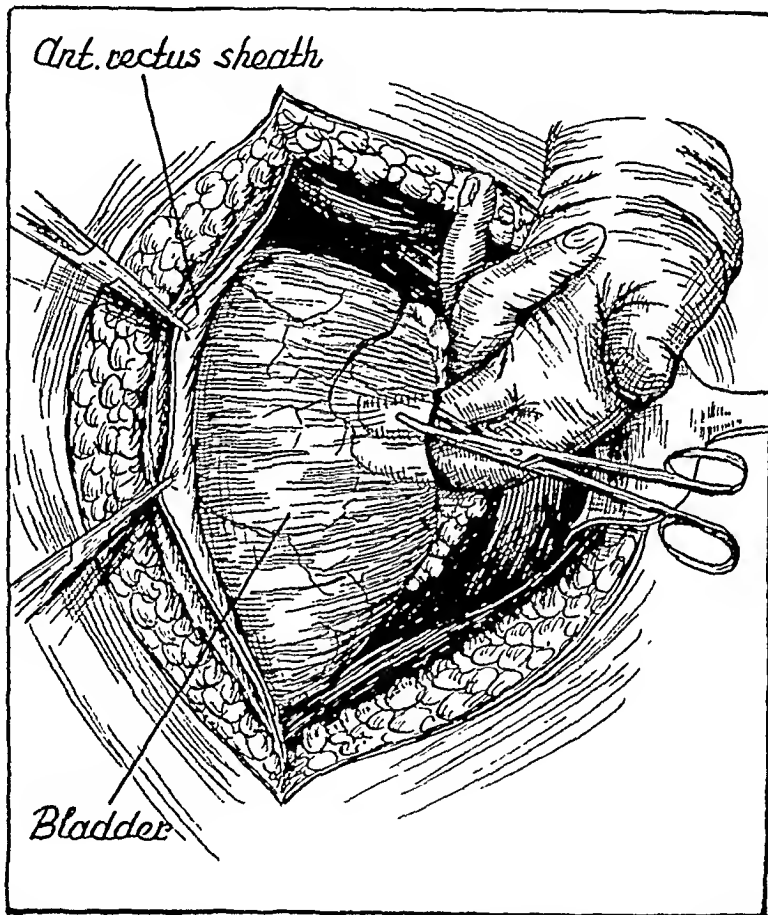


Fig. 2.—The index and middle fingers are insinuated into the left paravesical space in region of chicken yellow fat tissue and the fascia is lifted off the underlying bladder. The direction of the incision of the fascia should be more downward than here represented to avoid injury to anterior peritoneal fold at top of bladder.

which contains within its two folds the anterior peritoneal fold. (16) By traction upward on this flap, and countertraction downward on the bladder, the fascia connecting the anterior peritoneal fold above to the bladder below will be made taut, and the bladder still further separated by incising this taut fascia for any desired distance. The left impervious hypogastric artery may be encountered in effecting this extension across the superior surface of the bladder. Clamp and cut it. (17) The lateral and downward displacement of the bladder should be sufficient to place a vertical incision in the uterus practically in its midline. (18) Inspect peritoneal fold for any evidence of injury; if any is found, repair it. (19) Richardson retractors to hold (1) the peritoneum retracted above and (2) the bladder below

are put in place and vertical incision made in the lower uterine segment or lateral retraction may be made and a transverse incision made in the uterus. (20) Protect the lower angle of vertical incision with gauze pad held in place by retractor and make incision in the midline under direct observation. Thus, no injury can be caused to ureter or any large vessels at the sides of uterus. If vertical incision is used, incise upward from the bladder. (21) Culture taken from open uterus. (22) Deliver infant. (23) Ergotrate given intravenously. (24) Apply "T" clamps to the edges of the uterine incision. (25) Placenta removed. (26) Uterus closed with running No. 2 chromic suture on round Mayo needle. (27) Uterine incision inverted with continuous Lembert suture, using chromic No. 2 on a round Mayo needle. (28) Refill bladder to test for integrity. (29) Place five grams of sulfanilamide in the wound behind bladder. (30) Cigarette drain placed in lower angle of retrovesical space. (31) Approximate the muscle with No. 00 plain catgut interrupted. (32) Close the fascia with No. 2 chromic continuous using cutting edge needle. (33) Close subcutaneous tissue with interrupted No. 00 plain. (34) Dermal Stewart stitch for skin. (35) Remove retention catheter. (36) Drain removed in 72 hours.

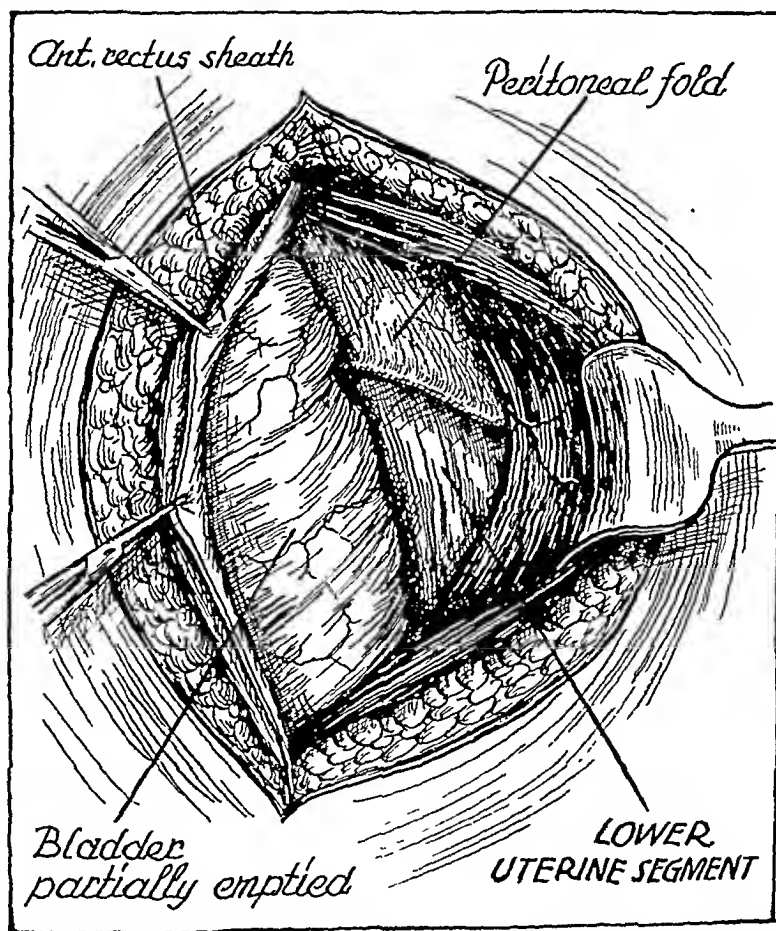


Fig. 3.—Bladder partially removed from lower uterine segment, showing bared triangular space. The upper border is the posterior peritoneal fold; mesial border, the partially emptied bladder; the lateral border, the parietes.

The drawing delineates the infraperitoneal nature of the rest of the operation, viz., remaining below the intact peritoneal fold.

Morbidity Rate and Complications

The average duration of labor for the entire group was 42.6 hours, and the average duration of labor with membranes ruptured was 29.8 hours. The intrapartum morbidity rate was 6.7 per cent. The peritoneal cavity was opened 44 times or in 27.5 per cent of the total. In the earlier cases included in this series, some few patients had the peritoneal cavity opened

deliberately in order to gain more operative room. Nine, or 5 per cent of the total, had the bladder injured, 8 of these occurred in the first 63 cases.

The postoperative morbidity in the entire group was 98, or 61.2 per cent. The standard of morbidity used was a rise in rectal temperature to 100.4° F. on any two readings following the first 24 hours, temperatures being taken every four hours.

There were 9, or 5.6 per cent, stillbirths or neonatal deaths. Thirty-nine, or 24.4 per cent, of the babies born weighed 3,800 grams or more.

There were three maternal deaths. One died in 1935 from infection, and another in 1936 from infection. There was one death in 1938 from hemorrhage.

Report of Fatalities

CASE 1 (History No. 21163).—A 23-year-old, white primigravida, a clinic patient, was admitted to the hospital on Jan. 24, 1935, and had her antepartum course complicated by a right pyelitis. After a labor of 82½ hours, with ruptured membranes for 34 hours, under spinal anesthesia supplemented by ether she had a paravesical cesarean section (Latzko) on Jan. 25, 1935. During the course of the operation the left ureter was severed and the bladder injured. A living 3,640 gram child was delivered. The patient had a septic postoperative course, with a clinical picture of general septicemia, rather than peritonitis, and died eleven days after the operation. At autopsy, there was found a large pelvic abscess at the place of operation, with separation of the cervical wound and left ureter. There was thrombophlebitis of uterine plexus and ovarian vein. An embolus (?) peritoneal abscess in the region of the splenic flexure was found. This is the twenty-seventh case in this series.

CASE 2 (History No. 27073).—A 29-year-old white primigravida with intrapartum temperature 103° F. After 55 hours of labor and 60 hours of ruptured membranes, she was delivered on Oct. 23, 1936, under spinal anesthesia, by a paravesical cesarean section (Latzko) of a stillborn 2,940 gram infant. During the course of the operation, the peritoneal cavity was inadvertently opened. She expired after about thirty hours, with a clinical diagnosis of peritonitis. No autopsy. This is the fifty-eighth case in this series.

CASE 3 (History No. 33298).—A 35-year-old white primigravida, whose labor was 104 hours, and no hours with ruptured membranes, was delivered under cyclopropane anesthesia by a paravesical cesarean section (Latzko) of a living 3,990 gram child Jan. 31, 1938. Immediately following the delivery of the placenta, a uterine hemorrhage occurred from an atonic uterus. The blood loss was estimated at 1,000 c.c. Patient expired on the table. No autopsy. The Latzko paravesical approach was used in all three cases.

There were 116 with an intact peritoneal cavity, of these 69, or 59 per cent, had a morbid postoperative course. Compare this with 66 per cent of those morbid with the peritoneal cavity opened.

With the average duration of labor as high as indicated in Table I, 42.6 hours, and with the average duration of labor with ruptured membranes in the whole group of about 29.8 hours, 11, or 6.87 per cent, had intrapartum morbidity. These figures indicate that the operation in our hands has been reserved for two groups of patients: (1) those who are potentially infected; and, (2) those who are frankly infected. No definition is required to cover the frankly infected patient. That is quite obvious. Some explanation or definition might be in order to cover the "potentially infected" patient. We believe that any patient in labor for a period of eight hours or more with ruptured membranes for a similar duration of time is potentially infected in the sense that pathogenic micro-organisms have already gained access to the amniotic sac; the longer and further this type of labor progresses, the more likely is the patient to be

TABLE I. THE INTRAPARTUM MORBIDITY RATE AND ANTEPARTUM COMPLICATIONS

TOTAL 160 CASES: 11 MORBID	
INTRAPARTUM MORBIDITY RATE OF 6.87 PER CENT	
Antepartum complications* in this series included—	
Early vomiting of pregnancy	1 case
Hematuria	1
Rheumatic heart disease	1
Pilonidal abscess	1
Hydrocephalus	1
Intercurrent eclampsia	1
Pyelitis	1
Adenoma of thyroid	1
Placenta previa	2
Syphilis	3
Attempted or failed forceps	3
Baggings	4
Failed medical inductions	4
Severe pre-eclampsia	5
Mild pre-eclampsia	8
Unclassified toxemia	9

*The antepartum complications listed were in no sense in any case an indication for the operation, the cases of attempted or failed forceps alone excepted.

TABLE II

YEAR	NO. OF CASES	AVER-AGE LABOR IN HOURS	AVER-AGE LABOR WITH RUPTURED MEMBRANES	PERITONEAL CAVITY OPENED	BLADDER INJURED	POST-OPERATIVE MORBIDITY	STILL-BORN OR NEO-NATAL DEATHS	BABIES OVER 3,800 GRAMS	MA-TERNAL DEATHS
				NO. %	NO. %	NO. %	NO. %	NO. %	NO. %
1931-1936	63	42	30.5	23 36.5	8 12.69	43 68.25	5 7.9	18 2.8	2
1937-1940	44	44	30.0	7 15.9	0 0	26 59.03	0 0	8 1.8	1
1941-1944	53	42	29	14 26.41	1 1.8	29 54.7	4 7.5	13 2.4	0
Total	160	42.6	29.8	44 27.5	9 5.6	98 61.25	9 5.6	39 24.4	3 1.87

TABLE III. A STUDY OF THE POSTOPERATIVE MORBIDITY WITH THE PERITONEAL CAVITY OPENED

Total number of cases	160
Peritoneal cavity opened	44 27.5%
Morbid cases in this group	29 65.9%
Morbid for 1-5 days	19
Morbid for 6-10 days	5
Morbid for 11-15 days	4
Morbid for 20 days	1

frankly infected. We further feel that this type of patient can best be served if she is to be subjected to a cesarean section by avoiding the contamination of the peritoneal cavity, and we accordingly utilize the operation when the patient has passed from the "clean stage" over to that of the "potentially infected" stage. We have considered some patients to be potentially infected even with apparently intact membranes if they have been in labor for many hours, and have had multiple rectal examinations. No explanation is necessary to cover the management of the frankly infected patient admitted to the hospital as such. The operation is not a procedure to be undertaken electively, and has no place in the management of a clean case by cesarean section. A word of caution is

in order about undertaking the operation in any and all frankly infected patients. Two maternal deaths in this study occurred in this type of patient.

The greatest technical difficulty encountered was the removal of the bladder and the freeing of the posterior peritoneal fold in two classes of patients. Multiparas with previous obstetric difficulty and apparently some old pelvic infection, and a few primigravidas also with old pelvic infection had very dense and fibrotic pelvic areolar tissue, and the structures did not separate easily.

Conclusions

Results obtained in 160 paravesical extraperitoneal cesarean sections are discussed, and a new paravesical approach to the retrovesical infraperitoneal area of the lower uterine segment is presented. (1) There were three maternal deaths in the 160 cases (two due to infection, one to hemorrhage); (2) the peritoneal cavity was opened 44 times (27.5 per cent). The bladder was injured 9 times (5.6 per cent) (eight times in the first 53 cases); (3) 98 cases (61.2 per cent) had postoperative morbidity; (4) the inadvertent opening of the peritoneal cavity did not impair the usefulness of the operation; (5) injury to the ureter occurred but once (case No. 27 in this series).

Speaking now specifically and directly of the technique here outlined, it is claimed: (1) relatively easy access is gained to the retrovesical area of the lower uterine segment; (2) identity of the posterior peritoneal fold is thus possible; (3) this retrovesical area can be enlarged under direct vision infraperitoneally; and, (4) sufficient room obtained to deliver baby of more than average size. (5) In the use of this technique there was no injury to any ureter or any large vessel at site of uterus; the ureter was never within the field of operation. There was no extension of incision into broad ligament at either side; no massive infection of pelvic cellular tissue occurred. There were no injuries to bladder in vesicovaginal area; there were no permanent vesicovaginal fistulas; there were no maternal deaths. (6) Adequate exposure for either a vertical or transverse incision in uterus is obtained. (7) The operation is well within the capacity of any competent obstetric surgeon.

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A CASE OF CLOSTRIDIUM WELCHII PUERPERAL INFECTION TREATED WITH PENICILLIN

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IN THE Johns Hopkins Bulletin of 1897, Dobbin published the first report of puerperal infection due to *Clostridium welchii*. Many cases have been described since, so that when Hill¹ wrote, in 1936, 84 cases were on record, to which he added 30, with a 63 per cent mortality in his own group. Sadusk and Manahan,² in reviewing the literature in 1939, found a mortality of 85 per cent for patients not treated with specific antiserum, and 47 per cent when treated with it. Infections with the gas bacillus may follow the birth of a viable fetus or may follow a spontaneous or, more commonly, a criminal abortion. Sixty to 75 per cent of puerperal *Cl. welchii* infections are said to be post abortal.

Clostridium welchii, more commonly known as the "Gas Bacillus," is a short, thick, spore-forming, nonmotile rod which grows under fairly strict anaerobic conditions. The bacillus is found in soil, milk, water, dust, sewage, decaying animal and vegetable matter, and in the intestinal tract of man and animals, as well as a normal or pathogenic inhabitant of the human vagina.^{3, 4} "Stormy fermentation" of milk is its most characteristic cultural attribute with the formation of clot, acid, and gas. Two types of exotoxins may be elaborated a hemotoxin and a myotoxin, the pathogenicity of a particular strain depending upon their elaboration. The organism is highly invasive.

Pathologically, puerperal gas gangrene may vary from a very mild infection, limited to the superficial layers of the endometrium and decidua and any retained products of conception, to a very severe infection involving the whole uterine musculature. From this, it spreads by direct extension or through the lymphatic channels to the peritoneum; invading the blood stream, it may metastasize to all the muscles of the body. The milder cases carry a good prognosis, but the more severe ones are associated with an extremely high death rate.

A typical, severe, Welch bacillus postabortal infection presents a characteristic picture: A patient who is acutely ill, yet mentally alert. She runs a low-grade temperature, associated with a tachycardia out of proportion to the fever. There soon develops a striking, and when once seen, a never-to-be-forgotten, icterocyano-sis. Signs of marked hemolysis with hemoglobinemia, hemoglobinuria, and anemia rapidly become evident. Milder cases may display only jaundice, without the serologic or urinary evidence of blood destruction. Still others display symptoms far removed from the original focus of infection in the genital tract; these are pain in the deep skeletal muscles, and an overwhelming toxemia. This syndrome is due to the myotoxin of the *Cl. welchii*, and death follows within a few hours of its onset.

The infection which follows the delivery of a viable fetus is more difficult to diagnose, but, in the main, more closely resembles cases of metastatic gas gangrene, than those in whom the hemolysis is the predominating symptom. However, the clinical picture may be so masked that the diagnosis is initially or entirely bacteriologic. More typically, pallor, tachycardia, peripheral cir-

culatory failure, sudden onset of severe uterine pain, with or without jaundice, are the symptoms leading to the suspicion of such a gas bacillus infection.

The importance of the early diagnosis of severe gas bacillus infections with their rapidly fatal outcome in most untreated cases is quite obvious.

There is much discussion in the literature about the necessity of surgical intervention, either by curettage or by complete excision of the infected uterus.⁵ Hill¹ and some others recommend the early, careful curettage of the uterus if the infection does not seem to have spread beyond the superficial layers of the decidua. If physometra, either alone, or with peritonitis, exists, then immediate total hysterectomy is indicated, according to them. It must be borne in mind that this advice was given before the sulfonamides or penicillin came into clinical use.

Once the diagnosis has been established, supportive and specific therapy must be begun without delay. General, supportive treatment consists of forcing fluids, both orally and parenterally, in anticipation of oliguria or complete anuria; repeated whole blood transfusions; administration of alkalis to combat the acidosis created by the organism, and to raise the pH of the blood in order to make the bacterial toxins less stable, and further, to alkalinize the urine in order to prevent precipitation of acid hematin in an acid urine. Finally, an attempt must be made to combat a renal shutdown, if it should occur. General treatment as outlined is important but, without the use of more specific therapy, only a 15 per cent cure is realized. The value of the *Cl. welchii* antitoxin is undoubted; it is administered intravenously and intramuscularly. It should be stressed that delay in initiating its use, inadequate dosage, and too early cessation of the anti-serum is almost tantamount to not giving it at all.

After the introduction of the sulfonamides in 1937, Bohlman⁶ and Kennedy⁷ individually reported the successful use of sulfanilamide in the treatment of surgical infections due to the Welch bacillus. Sadusk and Manahan,² noting the experience of these workers and others, were the first to report dramatic results in the treatment with sulfanilamide of puerperal infection caused by this organism. Hunt,⁸ in a review of the literature of chemotherapy in obstetrics and gynecology during the five years prior to 1944, concluded that the sulfonamides were of definite value in the treatment of infections of the parturient genital tract caused by the *Cl. welchii*, but pointed out that they must be given early, in large dosage, concomitantly with their specific antiserum.

A new and much more promising chemotherapeutic agent for *Cl. welchii* has recently been added to our drug armamentarium, namely, penicillin. Experimental work by Hae and Hubert,⁹ and McIntosh and Selbie,¹⁰ has shown the effectiveness of penicillin in the treatment of experimentally induced *Cl. welchii* infections. Penicillin was shown to be much more effective than other agents such as proflavine, the sulfonamides, tyrothricin, zinc peroxide, zinc oxide, and hyperol (hydrogen peroxide and urea). Efficiency varied directly with the time interval which elapsed from the onset of the infection to the onset of therapy. A therapeutic dose of penicillin given subcutaneously to mice at the time of intramuscular inoculation with the gas bacillus protected 98 of 100 mice so infected.

Since this experimental work, penicillin has been successfully used in the treatment of clinical cases of gas gangrene. There are not many reports in the literature of penicillin therapy of gas bacillus infections, but all relate dramatic results following its use. McKnight, Lowenberg, and Wright¹¹ were apparently the first to report a human case. Gas bacillus infection set in following a compound fracture of an arm in a 7-year-old girl. All routine

therapy was used, specific antitoxin, sulfanilamide, and amputation with little improvement, while awaiting the arrival of penicillin by plane. Dramatic results followed the intravenous administration of penicillin. McAuley and Gearhart¹² reported the successful use of a continuous intravenous drip of penicillin for twelve days with a total dosage of 1,580,000 units, after the unsuccessful use of sulfadiazine. This was in a case of gas gangrene following a simple, comminuted fracture of the femur. Pickett¹³ reports an accident occurring to two soldiers: one suffered a compound comminuted fracture of the surgical neck of the humerus with extensive laceration of the arm and shoulder; the other, extensive lacerations of the calf contaminated by debris and dirt. Both were treated surgically plus the use of plasma and blood transfusions in conjunction with sulfonamide therapy, both orally and locally. Despite these measures, both patients developed severe gas bacillus infections which finally responded to penicillin. Total penicillin dosage in the former case was 6,680,000 units and in the latter, 1,525,000 units.

Kepl, Oehsner, and Dixon¹⁴ report the treatment of two cases of gas gangrene. In the first, gas bacillus infection followed a shotgun injury with the development of cellulitis which was treated successfully by the local application of calcium penicillin over a period of six days. In the other case, the infection followed lacerations of the arm by broken glass and was treated by guillotine amputation combined with systemic and local penicillin. These observers issue a word of caution, stating that penicillin is of most value when combined with timely surgical intervention.

A search of the literature reveals no further clinical reports on the use of penicillin in gas gangrene infections. It should be noted that all the cases were traumatic accidents with secondary invasion by the *Cl. welchii*. To our best knowledge, no case of postpartum or postabortal gas gangrene treated by penicillin has yet been reported, and it is the purpose of this paper to report the treatment of a patient who developed a severe gas bacillus infection following a spontaneous six-month abortion.

Case Report

L. M., a 30-year-old, married, white, graduate nurse entered the hospital on March 5, 1945, because of premature rupture of the membranes and a pregnancy of six months' duration. She was not in labor. Her last menstrual period had begun October 4, 1944.

Ten years ago, while a student nurse, she had had an amputation of the cervix because of its hypertrophy with protrusion of the external os through the vaginal orifice. In June, 1944, her first pregnancy ended in the spontaneous expulsion of a four and one-half-month fetus following a very sudden and profuse gush of blood. Her present pregnancy was similarly complicated by a sudden gush of blood six weeks before admission. The patient remained in bed for six weeks and was then allowed up. Two days later, her membranes ruptured and she was hospitalized in the maternity.

In the hospital, she leaked amniotic fluid for four days without the onset of labor. She was then transferred to the delivery room and her cervix exposed with a bivalve speculum under aseptic precautions. It was found to be closed. The patient was then returned to her own room. Two days later, she went into labor and after one to two hours, delivered herself in bed of a stillborn, unmacerated fetus, 30 cm. in length. The placenta was easily expressed with a blood loss of less than 50 c.c. The abortion occurred at 10:45 A.M. on March 10, 1945. At 8:00 A.M. on the same day, the temperature was elevated for the first time; it was 101° F. by mouth.

The following morning, March 11, 1945, she complained of headache, sweating, pains in the back and abdomen, and marked weakness. Her skin was deep bronze, her lips and fingernails cyanotic. The sclerae were yellow, and she passed port wine colored urine. The temperature and pulse were normal and the blood pressure was 120/80. The white blood count was 52,000, with 93 per cent polymorphonuclear cells. Blood serum drawn for

determination of the icteric index was red. Hemoglobin and red blood count which had been 60 per cent and 3.5 million, respectively, on admission, were now 54 per cent and 2.21 million. The urine was negative for bile but positive in a 1 to 400 dilution for urobilin. Intrauterine culture taken at 8:00 P.M. on March 11, 1945, was reported positive 12 hours later for *Cl. welchii*. The urea was 92 mg. per cent (normal range 25 to 40 mg. per cent). The patient seemed to be very ill. A blood culture taken at the time of the uterine culture* remained negative throughout.

It was recognized that we were probably dealing with a case of *Welch bacillus* puerperal infection and, without waiting for the report from the uterine culture, 40,000 units of penicillin were given intramuscularly at 9:00 P.M. on March 11, and 20,000 units every three hours intramuscularly, from then until a total of 1,200,000 units had been given. Five hundred cubic centimeters of citrated whole blood were given on March 11 and repeated on March 12, March 13, March 15, and March 19.

Jaundice decreased promptly, and the patient felt better the day after penicillin was started. Actual recovery, however, was prolonged. The blood urea continued to rise in spite of the adequate output of dilute urine, reaching a peak of 191 mg. per cent on the eleventh day and returning to normal twenty days later. On the seventh day, the blood pressure rose to 185/100, remained elevated for seven days, then returned to normal. The white blood count returned to normal, and the hemoglobin and red blood count after the five transfusions rose to 96 per cent and 4.5 million, respectively. The temperature and pulse, with exception of one rise on the fifth day, remained approximately normal. On the fifteenth day, the patient developed twitchings of the extremities that persisted in spite of sodium lactate and calcium gluconate intravenously. These twitchings continued intermittently for approximately two weeks. On March 21, 1945, the twelfth postabortal day, the phenolsulfonphthalein test revealed a total output of 25 per cent of the dye in two hours. On the sixteenth day, six days after penicillin was stopped, the temperature rose to 103° F., the patient had a sharp chill, and a catheterized specimen of urine was loaded with pus cells. A full-blown, colon *bacillus* pyelonephritis developed. This subsided in five days, during which 140,000 units of penicillin, and 10 grams of sulfasuxidine daily, were given. The other sulfonamides were thought to be contraindicated because of the elevated blood urea.

The patient left the hospital on April 15, 1945, thirty-seven days after onset of the *Cl. welchii* infection, with a normal blood pressure and urea. Her phenolsulfonphthalein test had risen to 60 per cent excretion in two hours, and the patient was able to concentrate her urine to a specific gravity of 1.015. See Figure 1 for clinical and bacteriologic studies.

Discussion

The case history presents a picture of a moderately severe, postabortal infection due to the gas bacillus. The probable etiological factor was the presence of ruptured membranes for five days before abortion occurred. There is no history of criminal intervention and, indeed, this can be completely ruled out from the history. The pulse and temperature were normal until the day of the abortion and remained essentially normal through the height of the infection. Signs and symptoms, however, were quick to assert themselves after the abortion, so that within 24 hours, the patient was markedly jaundiced, superimposed on which was a cyanotic hue, especially evident in the lips and nailbeds. The patient looked ill and became toxic and lethargic. Penicillin therapy was begun some thirty-four hours post abortion and 12 hours after the patient became so ill. In six hours after the initiation of penicillin therapy, the patient was clinically improved, and her overwhelming toxicity had almost completely disappeared.

*Through a misunderstanding in the laboratory, the original blood culture was not planted anaerobically for 12 hours after the blood was drawn. At this time, 1 c.c. of the diluted aerobic broth culture was then planted anaerobically.

Other typical clinical features were: (1) the high white blood count with the marked shift to the left, (2) port wine urine, (3) the sharp drop in hemoglobin and red count, (4) hemoglobinemia, (5) positive uterine culture of *Cl. welchii*. A subculture was made and $\frac{1}{2}$ c.c. was injected intramuscularly into a 285-gram guinea pig. The guinea pig died twenty hours after the inoculation and at autopsy showed: (a) serosanguineous gaseous exudate at the site of injection, (b) peritonitis with the same kind of fluid, (c) cultures of the fluid from the site of injection and in the peritoneal cavity showed pure *Cl. welchii*, (d) the vena cava and inguinal veins showed gas bubbles.

As previously stated, the response of the *Cl. welchii* infection to penicillin therapy was prompt and dramatic. The marked anemia was successfully combatted with frequent whole blood transfusions. Uremia, apparently due to massive blood destruction by the bacterial hemolysins, was quite persistent despite the forcing of the oral and parenteral fluids and in the face of an adequate urinary output. The pathology underlying the later development of hypertension and tetany are still unclear, but apparently responded to intensive calcium gluconate, intravenous fluid, and alkali therapy.

The question arises whether the result obtained might not have been even more satisfactory had a specific antiserum been used in conjunction with the penicillin, the latter to combat the organism itself, and the former to neutralize the toxins which had already been produced before the initiation of therapy.

Conclusions

A case of moderately severe postabortal puerperal infection with *Cl. welchii* was successfully treated with penicillin given intramuscularly in a total dosage of 1,200,000 units. The patient's condition improved within six hours after commencing therapy. The possibility that combined penicillin and specific antitoxin therapy may be more rational and potentially more effective is suggested.

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VAGINAL HYSTERECTOMY

A Record of Results Based on the Weir Technique

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THE increasing popularity within the last few years of vaginal hysterectomy, like total abdominal hysterectomy, is evidenced by the large number of publications appearing in the current medical journals. In spite of the usefulness or advantages of this operation, an occasional article will appear, not only overlooking the merits of vaginal hysterectomy, but condemning it.¹ In reviewing the history of this operation, one has to agree with Cogswell² that it has weathered transient periods of popularity and unpopularity.

Knowing that any so-called routine technique must be modified in each individual case, the description of a number of techniques and the end-results statistically by various operators or clinics obviously proves to be of inestimable value in evaluating the operation and adds to its refinement. Thus a description of our method and the end-results seem justified. However, we would not want to convey the idea that every case of uterine prolapse with cystocele, rectocele, and other accompanying lesions, such as urethrocele or enterocele, can be corrected by one type of hysterectomy. As Masson³ states, the treatment must embrace the same surgical principles employed in the correction of any hernia as found elsewhere in the body.

In reviewing our records from 1928 to 1942, there were 6,017 hysterectomies done. From this total, 3,641 were abdominal hysterectomies and 2,091 were supraervical hysterectomies. Three hundred and eighty-five vaginal hysterectomies were done, or a percentage of 6.39.

The history of vaginal hysterectomy is of marked interest and has been adequately covered in many excellent articles and monographs.^{4, 5} As stated by Emmert,⁶ most of the reports in the literature fall short of giving the percentage of failures, the undesirable sequelae which are bound to occur in some cases, regardless of who performed the operation.

The method employed on the Gynecological Service of University Hospitals varies with the individual operator. However, the ward service handled by the Resident Staff follows the technique of Dr. W. H. Weir. It is for this reason that only Dr. Weir's cases and those of the staff ward service with a similar routine technique have been reviewed. The number of cases embraced in this report is 205, of which 88 are private cases of Dr. Weir* and 117 are ward cases.

*The authors have had, through the kindness of Dr. W. H. Weir, complete access to his private records, and desire to thank him for his helpful criticism.

In reviewing the histories, the frequency of postoperative cystitis is, of course, striking. This condition, which practically always cleared up before the patient went home, is no doubt due to several factors such as: (1) the large number of cystoceles present at operation with residual urine, (2) postoperative catheterization or constant drainage, (3) the inevitable operative trauma to the bladder in dissecting it free from the uterus. Further, there were more unsuccessful or unsatisfactory results on the ward service than on the private. This is perhaps due in some degree to lack of skill, although there is strict supervision by the Chief Resident or a Departmental Head.

Description of Operative Technique

The cervix is first transfixed with a heavy silk or linen suture for making traction. This will not tear out and it is generally more satisfactory than any tenaculum forceps. The cervix is pulled as far down as possible, and a transverse semicircular incision made through the mucosa at the vagino-cervical junction. A short incision is made upward from this one in the midline and the two angles of mucosa are separated by sharp dissection from the underlying tissues around and on either side as far as the lateral fornix. A pair of blunt scissors can now be easily worked up under the vaginal mucosa to just below the urethra and the mucosa is then incised in the midline up to this level. The triangular flap of mucosa on either side can then be easily stripped off from the surface of the bladder far over on either side. The bladder is then dissected free from the anterior uterine surface and completely separated at the sides as well, so that it can be pushed up freely under the arch of the pubes, exposing the whole anterior uterine surface. The vesico-uterine peritoneal reflection is then opened from side to side, or this may be done later, after the lower pedicles have been tied and divided when the finger may be passed up behind the uterus and over the fundus. The exact relation to this peritoneal fold is then easily determined.

Traction is then made upward on the cervix, and the mucosa of the posterior fornix incised from side to side and Douglas' pouch opened. With a finger in this pouch and the thumb anterior to the broad ligament, the attachment of these lateral supports is easily identified. They are ligated with a double strand of chromic gut and divided close to the cervix, well inside the ligature. As soon as this pedicle is divided, the uterus comes down much more readily with traction. The tissues on the other side are ligated and divided in the same way. If the uterus comes well down, the remaining attachments on each side (the round ligament, tube, ovarian ligament, and ovarian artery) are ligated with a double strand of chromic gut and divided well inside the ligature. A clamp is placed on the pedicle to prevent its retraction, and the ends of the ligature cut so that no traction will be made on it, for fear of pulling it off. If the uterus is large or does not come down readily before ligating this pedicle, the fundus may be delivered posteriorly which will facilitate passing the ligature and tying the pedicle. A similar pedicle is ligated on the other side and the tissues divided, completing the separation of the uterus. If the tube and ovary are to be removed, the infundibulopelvic ligament is tied outside the tube and ovary, the tissues divided well inside the ligature, and the stump allowed to retract. In this case, the round ligament alone would represent the pedicle on this side. It would be ligated and divided close to the cornu. The two upper pedicles are then stitched together with a double No. 2 catgut, and this stitch includes the peritoneal edge of the vesical reflection. If the pedicles are very lax, they may be overlapped. The prolapsed bladder is now pushed up above these sutured pedicles and the base of the bladder, at a point just above the trigone, is sutured to these united pedicles with a single ligature. The cystocele will then be held up at the proper level, but is further supported by later suturing the pubovesical fascia from either side in the midline.

The two lower pedicles are then sutured together with a double strand of chromic catgut, which also includes the peritoneal edge of the cul-de-sac, first dissecting out and

excising the sac of any existing enterocele. The ligatures uniting the two upper and the two lower pedicles may be tied together approximating all the supports in a single sling, but in the rare cases in which drainage is used, a cigarette drain is inserted into the cul-de-sac, between the two, and they are not tied together.

The pubovesical fascia, just beneath the mucosa on either side is united in the midline beneath the bladder by several chromic gut sutures from just beneath the urethra down to the former site of the cervix. The excess mucosa is then resected on either side, and the remainder sutured in the midline with a continuous stitch. Repair of the perineum, in the usual way, completes the operation.

Advantages and Disadvantages

There are some inescapable advantages for vaginal hysterectomy such as:

1. The total operation, viz., the hysterectomy, repair of the anterior vaginal wall, correction of cystocele, excision of enterocele if present, perineorrhaphy can be done at the same time.

2. Patient is not subjected to such a long operation as when the abdominal procedure is done.

3. It is a total hysterectomy, thereby removing the cervix and relieving the patient of a chance for subsequent development of carcinoma of the stump. Further, according to J. Hamilton,⁷ when subtotal hysterectomy is done the chances for a prolapse are greater than with a total hysterectomy.

4. Morbidity is less.

5. Operation may be carried out with general, local, perineal pudendal block, or spinal anesthesia.

6. Patient may be up sooner.

7. Pulmonary complications are less frequent.

8. Operative time is shorter.

There are certain disadvantages not to be overlooked, and certain conditions make the operation more difficult, such as:

1. Large tumor (myoma) of the uterus offers difficulty. In these cases, we prefer the abdominal route, although many men choose morcellation and piecemeal extraction per vaginam.

2. Small vaginal outlet which interferes with good exposure makes ligation of vessels and reconstruction of the pelvic sling difficult. The operation is often longer and more traumatic to the patient than the abdominal. The clamp method or a Schuchardt paravaginal incision will often obviate this condition. However, we do not use the clamp method at the University Hospitals.

3. Adherent or fixed uterus due to pelvic adhesions, endometriosis, and those adnexal lesions too difficult to remove by the vaginal route.

4. Rarely, but occasionally, previous suspension may render the operative procedure difficult.

Since it is not an infrequent observation to find cystocele, rectocele, prolapse uteri, and even procidentia, in nulliparous women, the finding of a slight degree of prolapse after vaginal operation should not be too severely criticized. The failure to correct an enterocele, urethrocele, etc., at time of operation is simple negligence, and unnecessarily subjects the patient to another operation. Two cases of enterocele on the ward service were overlooked at the time of operation.

Postoperative Care

A moist iodoform gauze pack is placed into the vagina for 36 hours and a straight male catheter in the bladder. Both are removed at the same time. Prostigmine (1:4,000) ampules is given every four hours for two to three days with rectal tube. This increases prothrombin time and relieves postoperative distension, and facilitates emptying the bladder. Supportive measures, such as hyperventilation, blood transfusion, etc., are given when

indicated. Morphine, demerol, or dilaudid are given for pain during first three or four days, and later, codeine. Barbiturates are not given freely to elderly patients. Ample fluids are encouraged, usually from 2,500 to 3,000 c.c. daily. Movement of extremities is encouraged. Patients sit up on the seventh day, are out of bed on the eighth, and home on the twelfth.

Discussion

In reviewing the vaginal hysterectomies, we have reported only 207 cases from ward service and those of Dr. W. H. Weir. The technique as described, we feel, has given very satisfactory results. In using the suture method, adequate room (outlet) with good exposure is necessary. We believe that suturing the base of the bladder to the united upper pedicle is an important feature of this technique. Plication of the uterosacral ligaments is extremely important to prevent recurrent prolapse and enterocoele. This step is overlooked by many operators.

Two postoperative deaths occurred, one due to pulmonary infarct (ward case) and one to cardio-vascular-renal disease, for which the operative risk was poor and the patient died six weeks after operation.

Scrutinizing the three enterocoeles: two were overlooked or not diagnosed at time of operation; one was recurrent and hence must be charged up to an incomplete or inadequate operation. The two cases overlooked were subsequently operated upon and, although subjecting the patient to a second operation, the end-results were successful. There was one very small vesicovaginal fistula which healed spontaneously four months after operation.

Postoperative pelvic abscesses only prolong the hospital stay of a patient. Fortunately this occurred in only one case. We believe that pelvic infections or abscesses are rare because of careful preoperative vaginal toilet. We cleanse the perineum and vaginal vault with tincture of green soap, followed by painting with iodine and 70 per cent alcohol after draping. Also, with traction sutures, the cervix is practically closed. Postoperative hemorrhage is not an infrequent occurrence according to Danforth.⁸ There was but one in this series requiring a secondary operation.

TABLE I. RESULTS

Total vaginal hysterectomies—1928 to 1942		385
A review of private and staff patients from the Gynecological Service		205
Unfollowed		7
Follow-up examination from two to ten years		192
Mortality	2	1.04%
Recurrent rectocele	5	2.60%
Recurrent cystocele	7	3.64%
Prolapse of vaginal vault	4	2.08%
Pelvic abscess	1	.52%
Shortened vagina	4	2.08%
Urethrocele	2	1.04%
Stress incontinence	4	2.08%
Enterocoele:		
a. Overlooked at time of operation	2	1.04%
b. Recurrent	1	.52%
Vesicovaginal fistula	1	.52%
	17	17.17%
Corrected		
1. Two overlooked enterocoeles—later operation satisfactory		
2. Vesicovaginal fistula healed spontaneously, making 14 unsatisfactory cases or		7.07%

Conclusions

1. That vaginal hysterectomy is a procedure of inestimable value is hardly debatable.
2. A review of vaginal hysterectomies at University Hospitals of Cleveland has been presented with the follow-up end results.
3. A description of the method employed by Dr. W. H. Weir has been given in detail.
4. Only the patients of Dr. Weir (private), and the ward employing a like routine technique, have been used.
5. In performing any operation, the operator should utilize the procedure best suited to the individual patient.

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THE MEASUREMENT OF THE DIAMETERS OF THE PELVIC OUTLET*

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IT IS a matter of general agreement among those doing obstetrics that a knowledge of the pelvic diameters of the *inlet* is a sine qua non for the scientific conduct of a case of labor, and yet very frequently the outlet measurements are honored in the breach.

It is the purpose of this paper to urge first, that the study of the outlet diameters be not neglected, and second, to describe a manual method for their estimation, much simpler than any heretofore described. While the importance of the outlet measurements is not as great as those of the inlet, since the incidence of contraction at the outlet is not as frequent as at the inlet; nevertheless, if all the disasters which have resulted from ignorance of the outlet diameters could be tabulated, their importance would be emphasized in no uncertain terms.

There is no question that contractions at the inlet have presented a much more simple problem than do those at the pelvic outlet, since the inlet diameters can be sufficiently accurately measured manually or by x-ray, while on the other hand the outlet diameters have in the past been found to be much more difficult to estimate. This is unfortunate, since grave damage to the mother and baby may well be the result of ignorance of the outlet measurements. While the x-ray measurements are of great value, it goes without saying that many women cannot have the benefit of such a study because of the expense involved or because of the lack of a roentgenologist capable of making the measurements.

It is clear that, if a mistake occurs in pelvic brim measurements, there is always time to perform a cesarean section before the labor has advanced to the point of exhaustion of the mother and damage to the baby. If, however, the outlet is the area of contraction, as is the case in funnel pelves, dystocia may often not be evident until the labor is of many hours' duration, too late for section and too late except for a difficult forceps, or even a destructive fetal operation. Every obstetrician of experience will remember cases in which the early labor progressed in a normal manner but, when the passage of the head through the outlet was attempted, progress ceased and a difficult extraction was necessary, to say nothing of the frequently severe injuries to the soft parts of the mother. It is our belief that in many cases of marked outlet contraction, a cesarean operation should be done before labor, since if it is justifiable to open an abdomen for many conditions not immediately threatening life, an everyday

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occurrence, it is certainly justifiable to do a cesarean section to save the life of a baby and/or to avoid damage to the pelvic structures of the mother, often difficult to repair and in any event requiring subsequent operation.

The senior author's interest in the contractions of the pelvic outlet dates back over forty years to a case reported at the time in the late lamented University Medical Magazine.¹

This patient, a doctor's wife, had an ample pelvic inlet, and the labor was rapid and easy until the outlet was reached. Here for a while there was delay with marked elongation of the perineum comparable to the lengthening seen in persistent occiput in the hollow of the sacrum. Then a small round hole opened well back of the fourchette near the anus. In this case, the outlet transverse diameter was so short, or, in other words, the area of the anterior triangle was so diminished that the head was forced to be born through the posterior triangle.

Ever since this experience, which took place before Whitridge Williams' work on the pelvic outlet, we have been impressed with the great importance of the measurements of the pelvic outlet, and have made the outlet transverse estimation an integral part of prenatal examination. However, this one measurement, while it gives information of great value, is by no means all that should be obtained, as will be seen in a moment.

Breisky² (1870) was one of the first to emphasize the importance of the outlet measurements, and he invented a special instrument for the measurement of the transverse diameter. But his measurement of the pelvic outlet consisted of only two diameters, namely, the anteroposterior or sacro-pubic diameter between the lower edge of the symphysis and the sacro-coccygeal joint, and second, the transverse diameter between the inner surfaces of the tubera ischii.

Now it must be remembered that, while the pelvic outlet is formed by two triangles, the anterior and the posterior, having a common base which is the just mentioned transverse diameter, the two triangles are not in the same plane, being joined at their common base at an obtuse angle.

Champneys, as long ago as 1884, stated that neither the intertuberous diameter nor the anteroposterior diameter is an accurate criterion of the possibility of delivery. The measurement really needed, but which he said cannot be obtained with accuracy, is the space between a line joining the tubera ischii and the tip of the sacrum. This measurement suggested by Champneys is nothing else than the altitude of the posterior triangle which is now known as the posterior sagittal diameter, and which we believe can be easily determined by our method to be described.

The measurements of the outlet of the pelvis which should be taken routinely are: *first*, the transverse diameter between the inner surfaces of the tubera ischii; *second*, the anterior sagittal diameter, i.e., the distance between the middle of the transverse diameter and the symphysis; *third*, the posterior sagittal diameter, i.e., the distance between the sacro-coccygeal joint and the middle of the transverse diameter; and *fourth*, the pubic angle formed by the junction of the rami of the pubis.

In order to determine the transverse diameter, the senior author invented, many years ago, a very simple little instrument which is portrayed in the last edition of the textbook on obstetrics of the late Dr. B. C. Hirst.

By inserting this instrument between the tuberosities, the examiner is able to obtain an exact measurement, and without the aid of an assistant, which is of great advantage. If the measurement between the tuberosities is 8 cm. or more, the birth prognosis very probably is good as far as the outlet is concerned, but in a nonnegligible percentage of cases of funnel pelvis, this diameter is contracted to such a degree that difficulties are to be expected. If there is too little space in the anterior triangle of the outlet, the posterior triangle must be utilized for the passage of the head. If the posterior triangle is large enough, birth may be satisfactorily completed, though often associated with great damage to the outlet soft parts, but if it is too short, very unfortunate damage to both mother and fetus is not unlikely.

Williams gives a table (Table I) indicating the approximate compensatory increases of the posterior sagittal diameter necessary for various degrees of transverse contraction:

TABLE I

A transverse diameter of 8	cm. demands a posterior sagittal diameter of	7.5
A transverse diameter of 7	cm. demands a posterior sagittal diameter of	8
A transverse diameter of 6.5	cm. demands a posterior sagittal diameter of	8.5
A transverse diameter of 6	cm. demands a posterior sagittal diameter of	9
A transverse diameter of 5.5	cm. demands a posterior sagittal diameter of	10

Ever since the time of Champneys, 1884, obstetricians have been attempting to evolve a method which will allow at least a proximate estimate of the posterior sagittal diameter. Many instruments have been invented as those of Klien, Williams, Thoms, Breisky, and others. They take the measurement of the posterior sagittal externally, deducing a small factor because of the thickness of the sacrum, but the points between which the measurements must be taken are not prominent, and the obtaining of anything more than an approximation of the true measurement is, to say the least, very problematic. Moreover, these instruments cannot be used without the aid of an assistant.

Technique

Our technique for the measurement of the postsagittal diameter is simplicity itself and is as follows: The instrument (Fig. 1) used to measure the length of the transverse diameter of the outlet is placed between the most prominent points on the inner surface of the ischian tuberosities, said points having been marked with ink. This measurement having been obtained, the index finger is passed *into the rectum*, and without difficulty the little depression at the junction of the lower end of the sacrum and the first coccygeal vertebra is located. It is an advantage to have the patient draw her knees up until the anterior surfaces of the femoral regions are in contact with the anterior abdominal wall.

The hand is raised slightly until the rectal finger is bisected by the imaginary line between the ink marks on the tuberosities. The nail of the other hand marks this point, as in taking the diagonal conjugata of the inlet and the pelvimeter gives the number of centimeters.

A modification of the method may be made as follows: The transverse measurement of the outlet between the tuberosities having been taken, the finger is introduced into the rectum and the little dimple which marks the junction of the lower end of the sacrum with the coccyx is palpated, then the instrument for the transverse measurement is again placed in position and the point at which it impinges on the rectal finger is marked by nail pressure, and this distance between said mark and the tip of the finger gives the length of the postsagittal diameter. This method for the measurement of the posterior sagittal is rendered easy by the fact, as shown by Breisky, that the transverse diameter crosses the upper edge of the anus. Through the vagina this measurement is impossible because of the perineal body, but if the rectal method is used it becomes marvelously easy, and it has given us so much satisfaction that we felt that it should become common knowledge.



Fig. 1.

One paper which we have found since we began our present technique missed our simple procedure by a very small fraction. The author of this paper was Hansen, who, in 1934, published his instrument for measuring the posterior sagittal directly. This instrument consisted of a rod with a ring at the distal end into which he placed the index finger, and then introduced finger and instrument into the rectum, and under guidance of the finger placed the end of the rod upon the junction of the sacrum and coccyx, reading off the number of centimeters on the scale upon the shank of the rod. Why, having gone so far, he did not realize that the rod was unnecessary, is hard to understand. In any event, such is the case, as we have repeatedly demonstrated.

For the complete measurement of the outlet, therefore, not only must the two diameters mentioned above, namely, the transverse and the posterior sagittal, be obtained, but also, as has been said, the anterior sagittal and the subpubic angle. To measure the anterior sagittal, the same method is used as for the postsagittal, namely, a finger in the rectum which easily reaches the junction of the pubic rami, then the imaginary line between the ink-marked tuberosities is noted and a nail mark is made where said line bisects the finger in the rectum, and the number of centimeters is shown by the pelvimeter. Having obtained this measurement, the estimation of the pubic angle, i.e., whether it is 90° or greater, or less than 90° is simplicity itself, since in an isosceles triangle the angle found by the juncture of the two equal sides must be 90° of the altitude, i.e., in this case the anterior sagittal is one-half of the base line, namely, the intertuberos diameter. If the anterior sagittal is less than half the base, the subpubic angle will be more than 90° ; while if the length of the anterior sagittal be more than half the base, the subpubic angle will be less than 90° .

The importance of the estimation of the angle formed by the junction of the pubic rami is that if the length of the pubic rami is increased the angle will be lessened, even though the base, i.e., the intertuberos diameter, is ample, hence the head will necessarily impinge more deeply than normal into the posttriangle.

Comment

The measurements just described, namely, the anterior and posterior sagittal diameters, together with the transverse diameter give a very definite picture of the capacity of the outlet, of great value in prognosis of labor and

the choice of treatment. A small amount of practice will enable anyone to make the measurements just described with more accuracy than by the use of the complicated instruments which have been devised for this purpose, and no one of experience will fail to realize the added comfort to the attendant and safety to the patient.

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Discussion

DR. ROBERT TAUBER.—Sometimes it is difficult to find the little dimple over the sacrocoxygeal joint when taking the posterior sagittal by inserting the index finger into the rectum. In these cases it is advisable to bring the hips of the patient beyond the edge of the table and to examine bimanually. The coeeyx can easily be moved and the joint palpated beyond doubt.

I would like to say also a few words about the measurement of the subpubic angle. The anterior triangle of the outlet is an isosceles triangle. The pubic rami are the equal lines and the angle between the pubic rami is the subpubic angle. The basis of the triangle is the transverse diameter which we can measure between the inner surface of the tuberosities. The altitude of this triangle is the anterior sagittal which forms with the transverse diameter an angle of 90 degrees. This right angle allows us to figure the exact size of the subpubic angle, because, according to the trigonometric rules, the tangent of the half of the subpubic angle is equal to the opposite side (which is the half of the transverse diameter) divided by the adjacent side (the anterior sagittal). Therefore we can obtain the exact size of the subpubic angle by the measurement of the transverse and the anterior sagittal diameter. What we need to know is only whether the angle is 90 degrees or less.

If the anterior sagittal is equal to one-half of the transverse diameter, the subpubic angle is 90 degrees.

If the anterior sagittal is equal to two-thirds of the transverse diameter, the angle is 74 degrees.

These two rules are easy to keep in mind, and the knowledge of the size of the subpubic angle, in addition to the measurement discussed by Dr. Nicholson, permits us to judge whether the outlet is big enough for a normal delivery or not.

DR. A. E. COLCHER.—Drs. Nicholson and Tauber have developed a simple bedside method of estimating the measurements of the anterior and posterior segments of the outlet. Its value lies mainly in the field of markedly frank disproportion. A test of labor is necessary to see whether the presenting part can be brought down to the pelvic floor. If it is not, then the measurement is of no value. If it is, then it is a little late for section and a difficult outlet procedure must be resorted to. If a narrowed outlet is present, one would surmise that the actual inlet and midpelvis would be similarly contracted. One does not section a case because of borderline outlet measurements. Therefore, a method giving the maximum of information is desirable. Such a method was described by Dr. Walter Sussman and myself in the *American Journal of Roentgenology*, February, 1944. This method embodies all diameters, and measurement of the subpubic angle can be read instantly from a prepared chart. We have found that an ample posterior segment of the outlet and an acute subpubic angle offer no obstruction. If the posterior measurement is narrow and the subpubic arch acute, a problem is presented.

DR. NICHOLSON (Closing).—I would first of all call Dr. Colcher's attention to the relative frequency of the funnel pelvis in denying his statement that "if a narrow inlet is present one would surmise that the pelvic inlet would be similarly contracted." This is really the reason for the presentation of this paper.

As stated, we hope that the simple method here given will lead those doing obstetrics to give greater attention to the outlet measurements. Our experience with this method has proven its dependability and but little practice will be necessary to enable anyone to become expert in its use.

It might also be said that a relative contraction at the outlet may be definitely an indication for a cesarean section, but of course the decision should be made very early in labor, long before the head has reached the perineum.

THE PSYCHOSOMATIC TREATMENT OF HYPEREMESIS GRAVIDARUM BY HYPNOSIS

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THE treatment of hyperemesis gravidarum is still a common problem in obstetrics. The numerous methods in use today are prima facie evidence that none have proved exceptionally successful, even though a wide variety of these methods have yielded relief in some patients.

Kosmak¹ states, "the cardinal fact to be borne in mind is that no routine method applicable to all cases can be recommended, but in each instance, particularly in the more severe type, consideration must be given to the individual patient." In other words, treat the patient and not the disease.

It is acknowledged by many investigators that the relief of nausea and vomiting of pregnancy may often be the result of unintended suggestion derived from the therapy, regardless which method is used. Such results are in agreement with the theory held by many that there is a definite psychic factor associated with this condition, and the principal feature is an underlying psychosomatic condition. These factors are responsible, in part at least, for most instances of vomiting during pregnancy. If they are allowed to persist they can cause this type to merge into the toxemic or pathologic type. For thirty years Sir Arthur Hurst² has been convinced that the so-called pernicious vomiting is always hysterical in nature. He rejects the theory that a toxic form of the vomiting of pregnancy exists and that the division into nervous and toxemic cases is fallacious. He states that nearly all cases are curable by psychotherapy alone. DeLee and Greenhill³ state, "A functional disturbance of the nervous system is at the bottom of many cases of hyperemesis. Hyperemesis is amenable to suggestion, and most of the cures we accomplish are due to it." Williams⁴ laid great stress on the fact that mental suggestion alone will cure over 50 per cent of all cases.

In studying this group of patients, we have learned that these individuals consciously have one attitude toward the pregnancy, while unconsciously they harbor a totally different one. Because a woman is constituted by nature to bear children, it does not mean she may wish to do so, even though she consciously professes a desire for pregnancy.

W. Menninger⁵ states, "One learns from psychiatric experience that many women have no interest or desire to have a child, many others have unconscious aversion to pregnancy but express conscious desires based on illogical, immature, or even irrational consideration. In either case, one may expect that the mother would suffer during pregnancy, and that the conflict would display itself in a total organism reaction, both psychological and physiological."

An important emotional attitude influencing the pregnancy state is the inability to adjust oneself to it, even though conscious acceptance of the pregnancy

is manifested. The vomiting which occurs is but an expression of unconscious rejection of the pregnancy in some women. Another group consists of women who have long desired pregnancy and who believe that nausea and vomiting are a real part of it. When one of these women misses a period she eagerly looks forward to the onset of the "morning sickness" to clinch the proof that she is really pregnant, and when it appears she gives it all the aid in her power.

For a thorough survey on the more important psychological stresses and strains associated with pregnancy and a few of the manifestations of these, the reader is referred to W. Menninger's^{6, 7} extensive study on the importance of pregnancy as one of the major experiences in the life of a woman, both psychologically and physiologically.

K. A. Menninger⁸ has outlined many other somatic manifestations by which a woman may indicate her unconscious repudiation of her femininity. Because hyperemesis gravidarum is common, every obstetrician should have a thorough knowledge of the dynamics of this problem and be his own "psychiatrist."

Since many of these patients have emotional conflicts which are repressed, hypnosis offers more rational approach than most of the currently utilized methods of treatment, either eliciting the underlying psychogenic factors responsible for the nausea and vomiting, or by raising the vomiting threshold of the patient. Since relatively weak suggestion has been partially effective in bringing relief, a type of psychotherapy, combining the use of more powerful suggestion as the main implement, would seem desirable for treating this condition. Such a method where such suggestion can be used is available in the form of hypnosis as used in medicine today. The use of hypnosis in ameliorating subjective sensations of an unpleasant nature has been shown for many years to be an effective form of therapy in medicine.

Certain functional disorders, especially in obstetrics and gynecology, as shown by Kroger and his associates,^{9, 10} lend themselves remarkably well to this form of therapy and should command the attention of the obstetrician. Because many of the successful results in treating the nausea and vomiting of pregnancy are obtained on the basis of suggestion, we have selected this condition for the possibility of demonstrating relief through hypnotism by means of which powerful and concentrated suggestion may be easily applied. We wish to emphasize that hypnosis alone is only a means toward treatment and, when combined with only a moderate degree of psychoanalytic skill and knowledge, it can be a much more rapid and effective treatment of hyperemesis gravidarum than any of the methods in use today. The intricate methods of Freud and the modern psychoanalytical school are seldom needed. Muniz,¹¹ Bramwell,¹² and other investigators have used this form of therapy successfully.

Methods and Results

Cases Treated by Hypnosis and Posthypnotic Suggestion

The following procedure was used in seventeen cases. After rapport, which may be defined as the dependence of the subject upon the operator, is established with the patient, hypnosis is induced. This is characterized by a state of gen-

eralized hypersuggestibility which may be two to five times that of the normal waking state. The technique and various states of hypnosis have been described by Estabrook,¹³ Erickson,¹⁴ Brenman and Gill,¹⁵ Dorcus and Shaffer,¹⁶ Schilder and Kauders,¹⁷ and Young.¹⁸⁻²⁰ Several excellent reviews of the literature on hypnosis and suggestion have been published.

The actual induction of the hypnotic trance is a simple procedure. A discussion of what the therapist intends to accomplish is a prerequisite to the actual induction. The therapist, speaking in a confident and monotonous tone, urges the patient to relax. Kraines,²¹ technique is as follows: "I want you to relax. Relax every part of your body. Now when I pick up your hand I want it to fall as a piece of wood without any help from you. (The examiner then picks up the hand and lets it drop to the couch.) No, you helped raise the hand that time; just let it be so relaxed that you have no power over it. (The test is repeated as often as is necessary for the patient to learn to let it drop.) That's the way. Now relax your legs the same way; just let them be limp. Now take a deep breath and let it out slowly. Now concentrate on your toes. A warm sensation starts in your toes and sweeps up your legs, abdomen, chest, into your neck. Now relax your jaws. Relax them more, still more. Now your cheeks; now your eyes. Your eyes are getting heavier and heavier. You can hardly keep them open. Soon they will close. Now smooth out the wrinkles in your forehead. Good. Now make your mind a blank. Allow no thoughts to enter. Just blank. You see a blackness spreading before you. Now sleep. Sleep. Sleep. Sleep. Your entire mind and body are relaxed, sleep, sleep. (This phrase is repeated several times in a soft and persuasive voice.) Your sleep is becoming deeper, still deeper. You are in a deep, deep, sleep." After two or three minutes of monotonous repetition of the above suggestions, the patient is told to raise her arm and that it will become very rigid. This state is called cataleptie. It is the most effective state for therapeutic suggestion.

The susceptibility to hypnosis is determined by at least three factors:

- (1) The subject's previous experience.
- (2) The hypnotist's ability.
- (3) The method of induction.

These three variables account for the wide divergence in statements made. Serog²² claims that 100 per cent of normal healthy men and women are susceptible to some form of hypnosis. In our experience, comprising several thousand cases of hypnosis, the incidence of success has been about 90 per cent. Nearly all investigators concur that suggestions are more often effective when the patient is in a somnambulistic state, which is a state of complete posthypnotic amnesia. Suggestions are made to the patient in this state that she will stop vomiting. She will ask for food and retain it, not only immediately but for the duration of her pregnancy. These posthypnotic suggestions last for about a month, and when repeated often enough the desired results may become permanent, as has been pointed out by Kellogg²³ and Patten.²⁴ These posthypnotic suggestions are, as Erickson²⁵ has described, separate hypnotic states arising spontaneously in the individual. All fifteen cases were relieved utilizing this method. Only

one treatment was necessary to bring relief to five cases, two to six treatments were necessary for ten cases. There were two failures; one patient could not be hypnotized, and in another, although light hypnosis was induced, the vomiting stopped for two days and then recurred, necessitating therapeutic abortion. The following case histories are typical of our methods and results.

Case Reports

Mrs. V. W., No. 237-716, Illinois Research Hospital, aged 29 years, Negro woman, para i, gravida iii, last menstrual period June 4, 1943, at term March 2, 1944; admitted to the Illinois Research Hospital July 26, 1943, with a history of severe nausea and vomiting, accompanied by epigastric pain since July 18, 1934.

The nausea and vomiting resulted in a fifteen pound weight loss. She was extremely nervous, weak, and complained of headaches.

Past medical history was essentially negative. Obstetric history; therapeutic abortion February, 1938, at three months because of severe hyperemesis gravidarum. Second pregnancy resulted in a normal infant at term June, 1939, but the first trimester was accompanied by extreme nausea and vomiting. Physical examination on admittance revealed a patient who was acutely ill with considerable somnolence and lassitude. The skin and conjunctivae had a yellowish tint. Blood pressure 132/94, icteric index 9.0 mg. per 100 c.c. blood, nonprotein nitrogen 24.0 mg. per c.c. blood, weight 108 pounds, and the temperature 99.2° F.

In spite of the usual therapy consisting of dietary restriction, sedation and parenteral fluids, the vomiting persisted. Deep hypnosis, accompanied by somnambulism was induced July 27, 1943, one day after admission. This resulted in a complete and dramatic cessation of the nausea and vomiting and the patient was able to eat her regular diet from then on. Patient left the hospital in excellent condition. Posthypnotic suggestions were given to her while she was in a deep hypnotic state that she would have no more nausea and vomiting, and that she would look forward to having her baby with a feeling of joy and happiness. On October 15, 1943, under hypno-analysis, the patient confessed that she did not desire the pregnancy because of her poor financial condition and the possibility that her husband might be drafted.

On November 12, 1943, she weighed 127, an increase of 19 pounds since her admission on July 26, 1943. She has had no nausea and vomiting since the first induction of hypnosis in the hospital.

Mrs. E. H., No. 17406, Cook County Hospital: Negro woman, aged 30 years, para ii, gravida iii, L.M.P. Jan. 1, 1943. Two previous admissions to the hospital of 35 and 16 days respectively for the treatment of hyperemesis gravidarum during the first two months of pregnancy. On April 11, ten days after release from the hospital, the patient was readmitted with the same symptoms as before. She now appeared acutely ill and moaned continuously because of pain and tenderness in the epigastrium. The reflexes were hyperactive, the blood pressure 140/80, physical findings were otherwise negative. Laboratory findings were as follows: red blood count, 4,350. The urine showed a 1 plus albumin and a trace of acetone. The treatment consisted of parenteral fluids, sedation, vitamins, a gradual increasing diet, and corpus luteum extract intramuscularly. After a few days of this treatment, the urine showed a 4 plus acetone and 1 plus albumin. The patient failed to improve clinically, often being most uncooperative and excitable, vomiting greenish mucous many times daily and feeling very despondent. On April 15, the sclerae became jaundiced, the muscles hyperirritable; she also complained of epigastric pain and a stiff neck. Medical consultation stated that this suggested liver damage. On this day the nitroprotein nitrogen was 27, chlorides 495, uric acid 2.4, calcium 10.2, phosphorus 2.13, icteric index 25, hemoglobin 78 per cent, red blood count 3.99 million, white blood count 10,200; bile was present in the urine. Calcium gluconate and cevitamic acid were added to the other parenteral medications. On April 16, the pulse varied from 80 to 116 and became weak and irregular. The jaundice,

hyperirritability, vomiting, and epigastric pain increased. Immediate therapeutic abortion was considered, but hypnosis was suggested as a last resort.

On this day she was placed in a deep somnambulistic state by one of us (W.S.K.). Strong posthypnotic suggestions were given to her that the vomiting would cease immediately, and that she would be able to eat and retain her meals. She was left in a deep hypnotic state for two hours with her right arm held in hyperextension and cataleptic. She was then awakened, and an obvious and dramatic change in her condition could be seen. Her apprehension and excitability were gone and she stated that she now felt greatly improved. On each of the next two days she retained three or four small feedings and thereafter larger ones. She was hypnotized daily for a total of six times by one of us (W.S.K.) and the intern, to whom rapport had been transferred. She improved steadily. The jaundice cleared up, the icteric index gradually returned to normal, and the pulse became regular. In ten days the patient was up and about and left the hospital in good condition. Thereafter she had an uneventful prenatal course and delivered spontaneously on October 19, 1943.

Cases Treated by Hypno-Analysis and Age Regression

It occurred to us that most cases of nausea and vomiting present a characteristic constitutional psychosomatic pattern which may be responsible for a lowered vomiting threshold. Because latent psychogenic factors contribute to the intensity and production of the more severe cases of vomiting, they must be determined by an exhaustive study of the personality. We have utilized age regression with hypno-analysis, which is a rapid form of psychoanalysis under hypnosis. The technique of hypno-analysis has been described by Hadfield,²⁶ Karup,²⁷ and Taylor.²⁸ The patient is regressed to a preadolescent age prior to the pregnancy. The patient is then slowly reorientated to her present chronological age. The development of emotional conflicts, personality changes, inhibitions, faulty attitudes toward pregnancy, or harmful habit patterns can easily be discovered. Appropriate suggestions are then made toward their removal. After the patient is reeducated by intensive psychotherapy under hypnosis, a cure may be effected readily. However, it must be emphasized again that hypnosis, when used in these cases, is only a means toward treatment, not the cure itself. It only effectively speeds up the entire process. We agree with Kraines²⁹ who states, "In the therapeutic suggestions it is not only important to suggest that the symptom clear up, but to suggest that the basic emotional difficulties be dealt with. Hypnosis thus becomes a valuable aid in enabling the patient to carry out the retraining of the personality as well as suggesting away the symptoms. Hypnosis which deals only with the symptom cannot obtain permanent remission, and the symptoms will recur until the basic cause of the symptom is removed." We believe that hypno-analysis and age regression can extract and use intimate facts from the subconscious mind which ordinarily would not be available to the physician with the patient in the wakened state.

Four patients were treated by hypno-analysis and age regression. Three to five applications were necessary to elicit the factors responsible for the symptoms of the four cases in our small series. Among the psychogenic factors responsible for the vomiting in one of the cases was an unhappy home life with impending divorce; the threatened loss of a career due to pregnancy was a factor responsible for the vomiting in another case.

The following cases are typical of our methods and results:

CASE 1.—Mrs. E. P., aged 31 years, white, para ii, gravida iii, L. M. P. June 22, 1941. On August 26, when about two months pregnant, she complained of severe nausea and vomiting. Physical examination was essentially negative. Past obstetric history: two normal full term pregnancies, with no nausea or vomiting during either pregnancy. Usual therapy consisting of dietary restriction, sedation, hormones, and strong waking suggestions were of no value. After one week of intractable vomiting, during which time the patient lost 12 pounds, hypnosis was induced on September 2, 1941, and repeated on September 5. The usual posthypnotic suggestions were given. The urine showed acetone 1 plus, albumin 0. Patient returned two days later and stated that she felt worse. At this time deep hypnosis was induced, and the patient regressed to the age of 30. The following salient facts were elicited. She was not in love with her husband and was extremely frigid during sexual intercourse with him. On numerous occasions during the past two years, she had extramarital relations with another man, with whom now she was very much in love. While in the hypnotic state she admitted that this man was responsible for this pregnancy. Under hypnosis it was made clear to her that the vomiting was a rejection of the pregnancy. Because she had divulged material that had been repressed, her strong guilt feelings would now disappear, and her secret would never be disclosed. She was reorientated to her present chronological age and awakened. As a result of this "mental catharsis" she felt very much relieved. Her nausea and vomiting promptly ceased the following day, and the remainder of her prenatal period was uneventful.

The above information could no doubt have been elicited without hypno-analysis, but it might have taken considerable time. The rapid cessation of the nausea and vomiting cannot be explained on any other basis.

CASE 2.—Mrs. J. K., aged 28 years, white, para 0, gravida i, L. M. P. April 15, 1942, at term January 22, 1943, had a history of nausea and vomiting of one week duration. On July 17, deep hypnosis was induced and posthypnotic suggestions were given that all nausea and vomiting would disappear. The patient returned in one week and stated that her symptoms, although milder, were still present. On January 24, deep hypnosis was again induced and the patient regressed to the age of twelve. The following facts were elicited: she had been a tomboy as a young girl and wished she had been a man. She married only because her family wished her to, and was not in love with her husband. Intercourse was extremely distasteful to her. It was only at her husband's wish that she became pregnant. She detested dressing up in feminine clothes, preferred slacks and mannish attire. Consciously, she denied any homosexual tendencies. Under hypnosis, induced on August 2, she stated that the reason for the nausea and vomiting might be due to the repudiation of her femininity and rejection of the pregnancy. The nausea and vomiting persisted. Under hypnosis on August 15, she agreed to give up her unconscious masculine tendencies and accept the child. The nausea and vomiting ceased and the remainder of her prenatal period was uneventful.

Discussion

In our series of 21 cases treated as described above, utilizing hypnosis as a method for controlling the neurotic tendency of the nausea and vomiting of pregnancy, the results are most gratifying.

Most of the patients were affected seriously enough to require hospitalization. No definite reason could be demonstrated for the vomiting. The usual methods of treatment consisting of dietary restriction, sedation, and parenteral fluids relieved the dehydration and inanition, but did not control the vomiting. One case (E. H.) described above, was so severe that immediate therapeutic abortion was considered.

The inconvenience of using hypnosis is relatively negligible when compared with other time-consuming therapeutic methods. The technique of hypnosis can easily be acquired by any physician. The mechanism of its therapeutic action in these cases is either that underlying etiological factors are discovered and effectively removed by suggestion, thereby raising the vomiting threshold, or else hypnosis and posthypnotic suggestion may establish a block in the nervous pathway between the gastrointestinal tract and the vomiting center in the higher sensorium. Heyer³⁰ has demonstrated the effect of hypnotic suggestion on peristaltic movements of the intestinal tract, and these can either be augmented or abolished. One of the explanations for this block may be that the effect of hypnosis is "synaptic ablation," states Estabrook.³¹ Kroger³² induced vomiting in normal patients previously conditioned by hypnosis; thus the entire vomiting syndrome of pregnancy can be reproduced by posthypnotic suggestion. This is additional evidence that hyperemesis gravidarum is hysterical in nature.

Hull³³ states, "Through hypnotism, one may have an effective control of the high centers and certain processes only feebly influenced by voluntary effort. These are possibilities that the ready control of such physiologic mechanisms might prove of value in the treatment of numerous somatic disorders." Evidence which demonstrates the effect of hypnosis in these conditions would probably require a more thorough type of investigation. From a practical standpoint, however, hypnosis offers a very valuable method to our obstetric therapeutic armamentarium in bringing relief to a group of patients who suffer considerably during pregnancy. This fact alone warrants extensive trial with hypnosis.

Our experience substantiates Estabrook's³⁴ contention that, "One of the most useful of all hypnotic phenomena, at least from the viewpoint of medicine, is that curious ability which the somnambulist has to recall long forgotten memories. This is the keynote to hypno-analysis, a branch of psychotherapy which is destined to assume more and more importance as the prejudice to hypnotism in this country diminishes. Hypno-analysis is slowly coming into its own. It is a tremendous timesaver."

Hypno-analysis and age regression elicit latent psychogenic factors from the subconscious mind which are responsible for the nausea and vomiting. In addition, the patient may be unaware of these or have no desire to tell them to the physician. By this means, the attention can also be directed to a given topic so that more ideas related to the causative factors may be elicited through the processes of association, thus facilitating the searching out of the vomiting complex and allowing the patient more insight for the causation of her symptoms . . . the process of reintegration. In several articles, the thorough work of Erickson,^{35, 36} comprising several thousand cases, has shown that, in competent hands, there should be no untoward reactions or risk following the use of hypnosis. The prejudice which has relegated hypnotism to obscurity as an unexplained phenomenon, and which may have been warranted years ago because of unscientific activities should now be

abolished, and an objective evaluation made of the use of this valuable form of treatment. In addition, through controlled experiments that were not available to the earlier investigators, much more can be learned regarding its therapeutic application.

Summary

Nineteen cases of nausea and vomiting of pregnancy of varying intensity, ranging from the exaggeration of physiologic vomiting to true hyperemesis gravidarum, who obtained little or no relief following a wide variety of symptomatic treatments, were completely relieved of their subjective symptoms following the use of hypnosis, either with direct suggestion or with hypno-analysis and age regression. All patients except two were completely relieved utilizing these methods.

This form of therapy may act either by raising the vomiting threshold directly or by preventing contractions from the gastrointestinal tract reaching the higher sensorium. Again, the method of eliciting latent psychogenic factors responsible for the nausea and vomiting and bringing these to the surface and integrating them into consciousness is also a convenient, time-saving, and most effective therapeutic procedure for permanently relieving this ordinarily refractory condition.

We believe that this valuable adjunct in the treatment of the nausea and vomiting of pregnancy should be utilized by obstetricians.

We wish to express our thanks to Dr. Fred H. Falls for the use of the clinical material and to Dr. William J. Dieckmann and Dr. J. P. Greenhill for the valuable assistance they rendered in the preparation of this manuscript.

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104 SOUTH MICHIGAN AVENUE

THE MECHANISM OF THE HISTIDINURIA OF PREGNANCY*

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SINCE Voge¹ first noted the histidinuria of normal pregnancy in 1929, over 100 medical articles have dealt with this subject. Most of these reports were stimulated by the work of Kapeller-Adler, who improved Knoop's bromination reaction² for urinary histidine and urged its employment as a chemical test for pregnancy.^{3, 4} Subsequent studies have shown beyond doubt that the iminazole compound excreted is actually l-histidine,^{5, 6} and that much larger quantities of this essential amino acid are excreted during pregnancy, at least from the eighth to the thirty-sixth week after conception, than in the non-pregnant state.^{7, 8}

It is evident that routine qualitative tests for histidinuria can never become an accurate means of diagnosing pregnancy, for, with refinements of technique, almost all urines become "positive" for histidine, and the concentration of histidine is influenced by the diet,⁸ by the specific gravity of the urine,¹⁰ and by the duration of pregnancy.⁷ Of greater interest would be the determination of the cause of the histidinuria, for this would furnish a basis for studying the reasons for its disappearance when pre-eclampsia or eclampsia supervenes.¹¹

Possible Causes of the Histidinuria

The only serious explanation of pregnancy histidinuria which has been advanced is that of Kapeller-Adler and her co-workers. In a series of articles, she showed that only the human species excretes histidine during pregnancy;¹² that liver tissue removed from pregnant women at autopsy does not readily metabolize histidine, while specimens from men or non-pregnant women—even those showing extensive liver damage—show marked histidase activity;¹³ and that the addition of 50 to 500 rat units of chorionic gonadotropic hormone to ground human liver in vitro inhibits histidase activity.¹⁴ She believes, therefore, that this placental hormone which is produced only by the human species inhibits the normal metabolic breakdown of histidine by the liver, thus resulting in its excretion. More recently, she has suggested that histidine disappears from the urine in pre-eclampsia because a large proportion of it is transformed by a tissue decarboxylase to histamine, and that the latter may be a cause of the toxemia.^{15, 16} Some doubt is cast upon these concepts when it is realized that the chorionic hormone does not show an in vitro inhibition of purified histidase,¹⁴ and that when the excretion of the hormone is at its peak in early pregnancy, the rate of histidine excretion may be very low in-

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†With the technical assistance of Miss Dean Mayell.

deed.⁷ Furthermore, Edlbaecher and Heitz¹⁷ have been unable to confirm the relative inactivity of histidase in the liver tissue of pregnant women.

Instead of postulating any alteration of histidine catabolism in pregnancy, it is possible that the histidinuria could be due to a "lowered renal threshold," that is, to an inhibition of the tubular reabsorption of histidine. If this were true, then the administration of histidine orally or intravenously should result in its excretion at normal or low blood levels. If the liver histidase were inhibited, on the other hand, then the administration of histidine should result in a greater and more prolonged rise in the blood level. The present study is an examination of these two hypotheses.

Measurement of Blood Histidine

While the bromination technique is specific for the iminazole ring, it is not sensitive enough to detect the low concentrations found in blood. The diazo reagents such as p-phenyldiazonium sulfonate (Pauly's reaction), and diazotized p-nitroaniline or p-chloroaniline produce strong colors with both phenolic and iminazole compounds, and the diazo color of blood filtrates has often been attributed to "blood phenols." Barae^{18, 19} and Schwarz and co-workers^{20, 21} have shown quite convincingly that the diazo color of blood is due almost entirely, if not exclusively, to histidine, and that the concentration in normal blood serum is about 1.5 to 2.0 milligrams per cent. Regardless of its origin, we have for the purposes of this study considered the initial fasting blood level as a blank, and deal only with those increases which followed the administration of pure histidine.* We adopted p-chloroaniline, the reagent suggested by Edlbaecher and his associates,²² and found that reliable results were given by a perchloric acid filtrate²³ of whole blood. Because the color development is influenced by other blood constituents, as well as by the pH and temperature, we always determined for each sample the increment of color produced by adding 0.05 mg. of pure histidine to an aliquot portion.

Method

Reagents:

1. Diazo Solution I: 0.5 Gm. p-chloroaniline and 5 ml. concentrated hydrochloric acid diluted to 200 ml. with distilled water.
2. Diazo Solution II: 0.5 per cent solution of sodium nitrite.
3. Diazo Reagent: mix 2 parts of solution I with 1 part of solution II just before use.
4. M/20 Sodium Carbonate: 0.53 per cent solution anhydrous sodium carbonate.
5. Histidine Standard: 6.175 mg. of l-histidine mono-hydrochloride in 100 ml. of 0.1 N sulfuric acid.

All reactions must be carried on with solutions which are below 5° C.

Procedure:

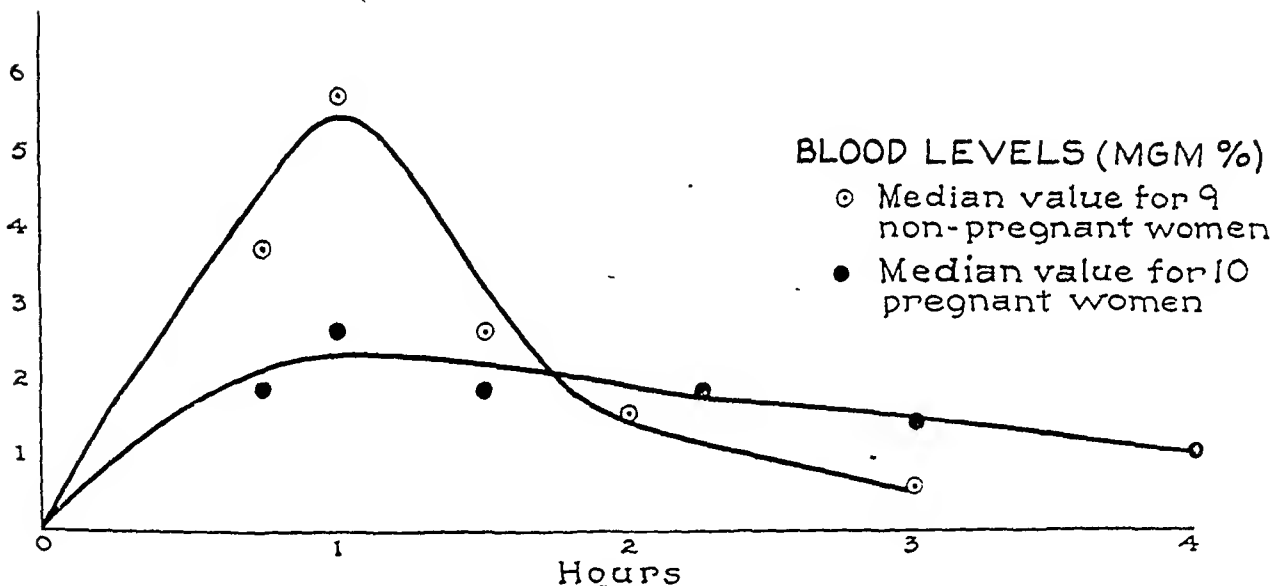
1. Dilute 5 ml. whole blood with 10 ml. distilled water, add 10 ml. 4.4 per cent perchloric acid, shake well and centrifuge.
2. Adjust the pH of 5 ml. of the supernatant fluid to 8.0 ± 0.1 with sodium hydroxide. Cool below 5° C.
3. Add 5 ml. of cold sodium carbonate solution and then 0.5 ml. of the diazo reagent drop by drop while shaking.

*The l- and d-histidine used in these studies was generously supplied by Mr. E. A. Wickham of the Hoffmann-La Roche Company.

4. Allow mixtures to stand in the ice bath for exactly three minutes, then add 10 ml. of butyl alcohol and shake vigorously.
5. Centrifuge and pipette off the butyl alcohol fraction.
6. Run a standard (consisting of 1 ml. of histidine standard solution to 5 ml. of filtrate) and a reagent blank at the same time.
7. Measure with a green (No. 54) filter in a Klett colorimeter, setting the zero reading against the reagent blank.

The Measurement of Histidine Excretion Rates

In all cases, a preliminary urine collection of known duration was obtained, and patients were instructed to drink one glass of water or lemonade every hour during the test. Following the oral administration of histidine, voided specimens were obtained at stated intervals, but following intravenous administration, hourly samples were collected by the use of an indwelling catheter. Because of the inherent errors of urine collections, especially during pregnancy, creatinine determinations were made by the method of Peters,²⁴ and the time intervals were adjusted by assuming a constant hourly creatinine excretion for any one individual.²⁵ In this way, an incomplete emptying of the bladder would not affect the final rate calculations. The urinary concentration of histidine was determined by our method previously published,⁷ and expressed as the quantity of histidine base excreted per hour or for an 8-hour period.



HISTIDINE EXCRETION (MGM)

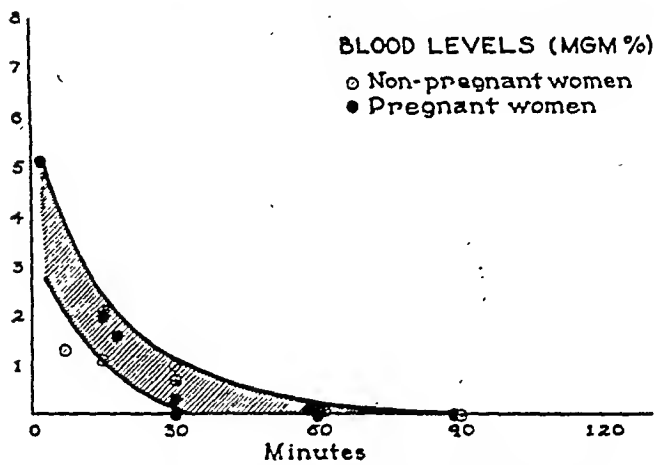
	No. Cases	8 hour period before histidine	8 hour period after histidine
Non-pregnant women	9	Range 0-54 Median = 23	Range 35-145 Median = 80
Pregnant women	10	Range 40-156 Median = 88	Range 84-550 Median = 314

Fig. 1.—Effect of 3.0 Gm. histidine orally.

Results

When 4 Gm. of l-histidine hydrochloride (equivalent to 3 Gm. of histidine) are given orally to normal fasting nonpregnant women, there is a progressive rise in the blood histidine followed by a slower decline as illustrated in Fig. 1. For any one individual the

EFFECT OF 0.74 GM. HISTIDINE I.V.

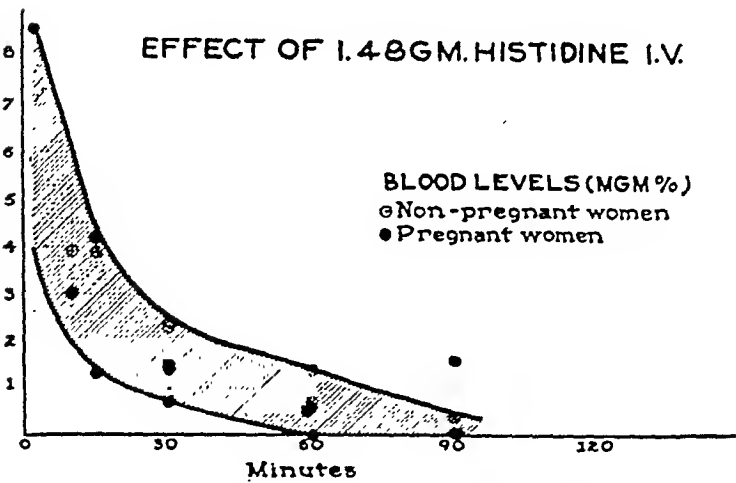


HISTIDINE EXCRETION (MGM/HOUR)

Pregnancy	Before histidine	After histidine		
		1 st hour	2 nd hour	3 rd hour
Not pregnant	1.4	2.8	1.8	0.7
Not pregnant	14.0	46.0	13.0	—
Not pregnant	0.	4.2	0.	0.
20 weeks	1.6	47.8	13.0	—
39 weeks	15.0	90.0	30.0	28.0

Fig. 2.

EFFECT OF 1.48 GM. HISTIDINE I.V.



HISTIDINE EXCRETION (MGM/HOUR)

Pregnancy	Before histidine	After histidine		
		1 st hour	2 nd hour	3 rd hour
Not pregnant	1.5	22.2	0	0
Not pregnant	2.2	25.0	150	14.0
28 weeks	1.3	25.2	170	13.0
32 weeks	10.3	48.5	350	—
35 weeks	50.0	262.0	41.0	—

Fig. 3.

rise and fall forms a smooth curve, but because the peak is attained at slightly different times in different persons, the median values do not fall exactly on the composite curve which is reproduced in Fig. 1. Nevertheless, there is a consistent difference between the blood curve of a nonpregnant and a pregnant woman, which is well illustrated by these average values. In normal pregnancy, the blood level rises more slowly, remains lower and persists for a longer period of time. That this is a characteristic of pregnancy is further emphasized by the fact that we have, in six additional cases, observed a gradual transition to the nonpregnant type of curve and to the lower excretion rates during the first eight days of the puerperium. At first glance, it might seem that this would indicate an altered rate of histidine metabolism during pregnancy, but it is obvious that the observed difference could just as well be due to a delayed absorption from the gastrointestinal tract. Indeed, the results of intravenous administration to be described below indicate that such is the case.

The significant finding from these experiments is that *a much higher rate of histidine excretion occurred at the same or even at lower blood levels in pregnant women*. This could mean only one thing, namely, that there is a "lowered renal threshold," or in other words, a diminished reabsorption of the amino acid by the renal tubules. As one may see from the data in Fig. 1, even the lowest excretion rate observed in pregnancy exceeds the average rate for nonpregnant women.

In order to differentiate between gastrointestinal and metabolic changes, several experiments were conducted wherein l-histidine was administered intravenously. A 10 per cent solution of l-histidine hydrochloride in saline was adjusted to pH 6.5, sterilized with a Seitz filter and given as a single rapid intravenous injection. No subjective symptoms or alterations of pulse rate or blood pressure have been noted.

Like the experiments conducted on dogs by Leiter,²⁶ the injected histidine disappears rapidly from the blood stream. Only a small proportion appears in the urine, showing that the greater part is utilized or destroyed. As illustrated in Figs. 2 and 3, the amino acid disappears *with equal rapidity in both pregnant and nonpregnant women*. If anything, the results of giving the larger dose of 1.48 Gm. by vein show a slower disappearance in nonpregnant women, though the cases are too few to establish this point. The ranges of blood levels as illustrated by the shaded areas include all but one or two aberrant values. With the larger dosage (Fig. 3) the shape of the curve is similar, but the blood levels are higher and persist longer.

If l-histidine is distributed in the extracellular fluids of the body-like galactose,²⁷ thiocyanate,²⁸ and similar substances, then an analysis of our data indicates that this equilibrium is rapidly attained within 10 to 15 minutes after intravenous injection. Some of the variations in blood levels are due to differences in body weight, but these variations cannot be correlated with the presence or absence of pregnancy. There is nothing in these data to support the contention that liver histidase is inhibited during normal pregnancy.

While there is an individual overlap, the highest excretion rate of 262 mg. in one hour occurred during normal pregnancy, and when allowance is made for the initial control rate, this represents an excretion of 15 per cent of the amount injected. The high rates in pregnancy and the lowest rates in nonpregnant women were observed at the same blood levels, again indicating an alteration of the renal threshold.

Discussion

Under normal circumstances, amino acids are freely filtered by the glomeruli and almost totally reabsorbed by the renal tubules. Doty²⁹ found that the dog's kidney reabsorbs 99 per cent of the histidine which passes into the glomerular filtrate. Pitts³⁰ believes that there is a specific mechanism for amino acid reabsorption and that such substances as creatine compete with certain amino acids for reabsorption. Our results indicate that pregnancy histidinuria is due to a diminution in this tubular reabsorption and not to a reduced rate of catabolism or utilization.

Is this phenomenon specific for l-histidine, or is it true of other amino acids? In some work to be reported later, we have observed that when the optical isomer d-histidine is injected, very high excretion rates result, but they are the same in both pregnant and nonpregnant women. The blood curves, showing a very slow metabolism of this unnatural substance, are likewise the same. We have administered 4 Gm. of tyrosine to pregnant women, but in this case there is no detectable excretion of tyrosine at all. It would seem, therefore, that the diminished tubular reabsorption for l-histidine does not apply to all related substances.

The histidinuria of pregnancy could then be due to a selective inhibition of the tubular reabsorptive mechanism, or to the competition of some other substance (such as the metabolite of a hormone) for reabsorption by this same mechanism. On this point we have no data, so that the immediate cause of the alteration in tubular function is as yet undetermined.

The work of Eiler, Althausen, and Stockholm³¹ has shown that a hormone (thyroxin) can alter markedly the rate of absorption of glucose, or other substance transferred by an active mechanism, from both intestinal or renal tubular epithelium. The present data indicates that l-histidine, which is also absorbed by an active mechanism, has a slower rate of transfer across both the intestinal and renal tubular barriers during normal pregnancy, and it is entirely possible that some hormonal change is responsible for both effects.

Summary

Simultaneous blood levels and urinary excretion rates of l-histidine were studied after its oral or intravenous administration. When given by vein, the histidine disappears from the blood stream with equal rapidity in both pregnant and nonpregnant women, which suggests that there is no interference with its utilization or destruction during gestation. Pregnant women, however, excrete a larger proportion of the histidine at the same or even at lower blood levels, demonstrating a "lowered renal threshold." When given orally, the same increased excretion rate at lower blood levels is noted during pregnancy, but the blood curves indicate a delayed absorption from the gastrointestinal tract. The decreased rate of absorption from both the gastrointestinal mucosa and the epithelium of the renal tubules observed in normal pregnancy may be due to the same inhibitory factor.

Pregnancy histidinuria has been attributed in the past to a hormonal inhibition of liver histidase. The experiments which we describe, however, support the alternative hypothesis that it is due to an inhibition or interference with the renal tubular reabsorptive mechanism for this particular amino acid.

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GRANULOSA-CELL TUMOR OF THE OVARY

Report of Five Cases With Premature Menopause (Amenorrhea) and the Recurrence of Menstruation

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ONE of the most impressive ovarian tumors is the granulosa-cell tumor. Although, since 1931, numerous articles have appeared in the scientific journals describing the tumor and its symptomatology, it is hoped that this report is not too repetitious. After removing a large granulosa-cell tumor of the ovary from a woman who had started menstruating again after an eight-year period of amenorrhea, the author decided to review the literature and study our records of University Hospitals in regard to certain aspects of this neoplasm. No detailed survey of the literature is given since there are already adequate reports in the journals.

To date, numerous articles and some 240 cases have appeared, many of which are individual case reports. The eagerness to report isolated cases is well understood when one considers the striking symptoms that often accompany this tumor. Especially is this true with granulosa-cell tumors in children.

Only twenty-one cases of granulosa-cell tumors were found in the records of the University Hospitals of Cleveland, and of these twenty-one cases, only two were diagnosed histopathologically as malignant.

Uterine changes most commonly mentioned with the granulosa-cell tumor are hypertrophy of the uterine musculature and hyperplasia of the endometrium. All of our cases in which the uterus was removed or in which a curettage was done showed these findings.

In dealing with a tumor such as the granulosa-cell type in which the three age periods reveal different types of symptoms, one can arrange the patients in three groups: (1) prepubescent or childhood (from infancy to puberty); (2) pubertal-adult (from puberty to menopause); (3) postmenopausal. The second group includes the period when normal menstruation would take place. This report is most concerned with the second group, although four cases in the third or postmenopausal group are mentioned. None of our cases fall into the first group, since we had no case less than 23 years of age.

The frequency with which granulosa-cell tumors occur as to decade in our twenty-one cases is similar to figures found in the literature. All agree that granulosa-cell tumors occur most frequently after menopause. Distribution of our twenty-one cases according to decade is as follows: 2 cases (9.5 per cent) in the 3rd decade; 9 cases (42.0 per cent) in the 4th decade; 7 cases (33.3 per cent) in the 5th decade; 2 cases (9.5 per cent) in the 6th decade; 1 case (4.7 per cent) in the 7th decade. The youngest patient in our series was twenty-three and the oldest sixty-nine.

In reviewing our case records, we were surprised to find five (23.8 per cent) of our patients gave a history of premature menopause (amenorrhea), followed by return of menstruation. Menstruation is used here as "uterine bleeding" regardless of whether it is normal menstruation or not. Hyperestrinism, as mentioned before, produced by the granulosa-cell tumor apparently accounts for the prevalent symptoms of menorrhagia or metrorrhagia (hypermenorrhea) or with the long periods of amenorrhea (polyhormonal amenorrhea).

Report of Cases*

CASE 1.—R. H., a 43-year-old Negro woman, was admitted to the gynecologic service of University Hospitals on April 3, 1944, with the complaint of profuse vaginal bleeding. In 1933, at the age of 35, she had stopped menstruating. At that time she experienced "hot flashes," dizziness, and other menopausal symptoms. In April, 1943, about one year before admission to the hospital, she began to menstruate again. This was irregular at first, with periods often lasting for one month. From November, 1943, bleeding continued throughout both November and December. With only three weeks' freedom from bleeding, menstruation again reappeared in the latter part of January and continued until operation. However, the patient was discharged from the hospital and remained home until readmission on July 9, 1944, to "gain strength and deliberate over the advised operation." One transfusion was given before she left the hospital. Aside from pelvic and abdominal findings and anemia, the patient was normal. Pelvic examination showed a large tumor mass the size of a four months' pregnancy. There was tenderness over the abdomen, but no rigidity or muscle spasm. No other suggestion of adnexitis was found. Temperature, 37.8° C.; pulse, 100, respiration, 20, blood pressure, 130/80.

Readmission: July 9, 1944: temperature, 37.4° C.; pulse, 84; respiration, 20; blood pressure, 130/80. Examination showed the same findings as described on her previous admission, but there was marked increase in size of the mass. Abdomen was extremely tender, and on the second day following a routine intravenous pyelogram her temperature rose to 40° C. She appeared extremely ill. Blood Count: white blood cells, 7,200; red blood cells, 2,630,000; hemoglobin, 58 per cent (Sahli). Urinalysis and microscopic precipitation test were negative. X-ray studies of kidney pelvis showed no radiologic evidence of a process of the upper urinary tract. Flat plate revealed rudimentary ribs on Lumbar 1 bilaterally. The neural arch of Sacral 1 was incompletely fused.

The patient's condition grew steadily worse, with the onset of nausea and vomiting. She refused to take food. The rise in temperature was concomitant with the complaint of "severe pain" in her abdomen. A rather sudden enlargement of the tumor mass followed the pre-x-ray routine of castor oil catharsis, precipitating the onset of fever, pain, and nausea, vomiting and marked enlargement of her abdomen.

On July 18, 1944, operation was scheduled for the following morning, and it was felt that the exacerbation of her condition was due to hemorrhage into a large ovarian tumor. On July 19, 1944, she was taken to the operating room and a large right ovarian tumor was removed. It measured 19 by 17 by 9 cm., and weighed 1,670 grams.

Pathologic Report.—"Granulosa-cell tumor of ovary, the seat of extensive necrosis, acute inflammation, and recent hemorrhage." The subsequent hospital course was uneventful, and she was discharged on the 11th postoperative day. She was given two transfusions of whole citrated blood, 500 c.c. each.

CASE 2.—S. R., a 45-year-old white woman, entered the gynecologic service as a private patient of Dr. R. L. Faulkner. Her complaint was vaginal bleeding for six months. She also gave a history of pain in her right side during the six months following the onset of her bleeding. Menstrual history: menarche at 16 years of age, regular every 28 days

*Case 5 is listed both as granulosa-cell tumor and theca-cell tumor.

to 30 days, with a period of amenorrhea for six and one-half years prior to the remenstruation that brought her to the hospital. The laboratory findings were essentially negative.

Examination on October 16, 1939, under evipal anesthesia, revealed hypertrophy of the posterior lip of the cervix with many nabothian follicles in its substance, and a tumor mass about the size of an orange on the right side. There were no other abnormalities.

On October 17, 1939, excision of the labial cyst, panhysterectomy, right salpingo-oophorectomy, and left salpingectomy were done.

Pathologic Report.—"Granulosa-cell tumor of ovary, follicular type. Physiologic hyperplasia of endometrium, mild. Chronic cervicitis. Hydrosalpinx, bilateral."

The hospital course was uneventful, and the patient was discharged on her thirteenth postoperative day.

CASE 3.—F. D. (patient of Dr. W. H. Weir), a 40-year-old white woman, entered the gynecologic service on August 7, 1940, with the complaint of menorrhagia following a period of two years of amenorrhea. Her menstrual history was normal, with menses occurring every 28 days until 1937, when amenorrhea was sudden. Seven weeks before admission bleeding started and had been continuous until operation.

On August 8, 1940, a panhysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The postoperative course was uneventful and the patient was discharged on the fourteenth postoperative day.

Pathologic Report.—"Granulosa-cell tumor of ovary. Fibromyoma of uterus. Adenomatous polyp of the endocervix. Chronic cervicitis. Fallopian tube—no pathologic diagnosis. Appendix—no pathologic diagnosis." The tumor (ovarian) measured 9 by 6 by 5.5 cm. and weighed 65 grams.

CASE 4.—L. T. (staff service), a 23-year-old Negro woman, entered the gynecologic service on June 14, 1937, with the complaint of a rapidly enlarging abdominal tumor, a 70-pound weight loss during the preceding 18 months, and profuse vaginal bleeding during the preceding year which often lasted for a month. Prior to onset of her present illness, she experienced eight months of amenorrhea.

The patient was extremely emaciated, weak, and severely anemic. Temperature 38.2° C.; pulse, 100; respiration, 25; blood pressure, 150/90. She had a slightly enlarged heart with loud systolic thrill at apex and systolic and diastolic murmur over pulmonic area. There was an irregular mass in the lower right quadrant and a definite fluid was imparted to the palpating hand. There was hydronephrosis of the right kidney and marked displacement of intestines and of kidneys. The amount of abdominal fluid was increased. X-ray examination of chest showed both diaphragms to be high in position, and a small soft shadow of increased density in the right first interspace just below the clavicle. Laboratory findings: admission white blood cells, 5,500; red blood cells, 3,110,000; hemoglobin, 30 per cent; phenolsulfonphthalein test, 80 per cent in two hours. On June 17, 1937, 1,500 c.c. of sero-sanguineous fluid was removed by abdominal paracentesis; this was negative for tuberculosis in guinea pig injection. The patient was given two transfusions prior to operation. The amount given was 1,250 c.c. whole citrated blood. On June 24, 1937, a perineorrhaphy, panhysterectomy, bilateral salpingectomy, and left oophorectomy were done under nitrous oxide and ether anesthesia. The tumor (ovarian) weighed 1,200 Gm.

Pathologic Report.—"Granulosa-cell tumor of ovary with cystic degeneration. Physiologic hyperplasia of endometrium. Chronic cervicitis."

After operation, the patient's condition improved. Her hospital course was uneventful, and she was discharged on her eleventh postoperative day.

CASE 5.—R. M. (surgical service, private patient of Dr. F. S. Gibson), a 40-year-old white woman, entered University Hospitals on May 19, 1942, with the complaint of resumption of bleeding after a period of eight years of amenorrhea. Patient was para vi, gravida vi. Aside from her menstrual history, her past history was essentially negative. Her menses began at 12 years of age, being regular and normal in amount until she was 26 years old. At that time they became irregular for a period of six years, then ceased

entirely. Five months before admission to the hospital she began to flow; this was intermittent with spotting almost daily. She had no pelvic or abdominal discomfort.

The significant physical findings were seborrheic dermatitis around the eyes, and cervical lymphadenopathy below old scar on right side of neck where previous draining sinus was present. Pelvic examination was not on record.

On May 20, 1942, under nitrous oxide and ether anesthesia, a supraeervical hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were done. The left ovary was cystic, and many adhesions were encountered, making the operation quite difficult.

Pathologic Report.—"The ovarian tumor measured 8 by 6.5 by 4 cm. and weighed 120 Gm." Histopathological report was "Atypical cystic hyperplasia of endometrium. Fibromyoma of uterus, theca-cell tumor and tuberculosis of one ovary. Atrophy of other ovary. Bilateral tuberculous salpingitis and unilateral hydrosalpinx. Appendix—no pathologic diagnosis."

Laboratory findings on admission: white blood count, 7,900; hemoglobin, 65 per cent. Urine was normal. Microscopic precipitation test was negative. Total proteins, 6.87 Gm. per cent; plasma protein, 3.75 Gm. per cent; globulin, 3.15 Gm. per cent.

The hospital course was uneventful, and the patient was discharged on her fourteenth postoperative day.

Comment

There are four patients in the series whose ages are 47, 46, 53, and 69 years in the charts reviewed. All four had reached menopause and experienced postmenopausal bleeding. The intermenstrual period of menopausal amenorrhea was 2 years, 3 years, 3 years, and 20 years respectively in the foregoing cases. All had granulosa-cell tumors.

We have presented the number of cases of granulosa-cell tumors found at the University Hospitals of Cleveland during the past ten years. The review of these cases was prompted by the finding of a recent case in which premenopausal amenorrhea occurred for a period of five years, after which menstruation recurred, making hospitalization necessary.

In reviewing the twenty-one cases of granulosa-cell tumors, we found nine cases of granulosa-cell tumors with a history of amenorrhea followed by re-menstruation. This is an incidence of 42.8 per cent. Five patients were classed as having premenopausal amenorrhea, or an incidence of 23.8 per cent. Four of the cases were classed as postmenopausal bleeding, or an incidence of 19.05 per cent.

That this phenomena of amenorrhea followed by menstrual return is the result of hormonal disturbance, has long been known. However, the exact mechanics of the amenorrhea in women who are far from their natural menopause, with a subsequent menstrual flow calls for further enlightenment. Kjaften states that the prolonged amenorrhea is due to the structures similar to corpus luteum or albicans in the tumor. As far back as 1930, he discussed the possibility for the first time of the enormous hormone activity of granulosa-cell tumors. At that time, he had no case to refer to, but, in 1934, he observed and cited a case of his own in which precocious adolescence in a 4-year-old child occurred with a granulosa-cell tumor.

The age incidence in twenty-one cases was as follows: 51.5 per cent in the third and fourth decade, 33.3 per cent in the fifth decade, 9.5 per cent in

the sixth decade, and 4.7 per cent in the seventh decade. The youngest patient in our series was twenty-three and the oldest sixty-nine.

The ages of the five cases reported were as follows: 43, 45, 40, 23, and 40 years of age.

Conclusions

1. A brief review of the literature has been presented, with a summary of five cases of granulosa-cell tumor from our own case records.

2. The five cases are summarized because of the finding of granulosa-cell tumor associated with premature menopause (amenorrhea with resumption of menstruation).

3. All patients were operated upon. Diagnosis made after operation on gross and by histologic means. Some only after microscopic examination.

4. From the total of twenty-one cases appearing on record, only two were diagnosed as granulosa-cell carcinoma.

5. Granulosa-cell tumors were catalogued according to age groups, namely: (1) prepubescent or childhood, (2) adult (those within the range of normal menstruation), (3) postmenopausal.

6. All twenty-one of our cases were in the second or third groups.

7. Case 1, R. H., menstruated twice after removal of granulosa-cell tumor, and at the present time is approximately three months pregnant.

8. Follow-up studies showed: all patients are living and have no evidence of recurrence.

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INFECTIOUS MONONUCLEOSIS COMPLICATING PREGNANCY

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MRS. R. H. D., para i, gravida iii, first presented herself for obstetric care on Sept. 5, 1944. Past history revealed acute nephritis following scarlet fever in childhood and one instance of surgery: a volvulus at the iliocecal area at the fourth month of the second pregnancy. The first pregnancy was spontaneously aborted after a fall in 1940. Except for the surgery, the second pregnancy was normal in every respect and terminated in full-term delivery in August, 1941.

The patient stated that her last menstrual period was June 27, 1944, and that she had had rather marked nausea and vomiting. General physical examination was negative; her weight was 110 pounds, which represented a loss of 3 pounds. Kahn test was negative; blood type A; red blood cells, 3,870,000 with 70 per cent hemoglobin. Pelvic measurements were adequate. The patient was placed on ferrous sulfate 0.324 Gm. three times a day, and vitamin capsules, and given the usual instructions. She was again seen on October 6 with normal findings except that the red blood count had dropped to 3,320,000 with 62 per cent hemoglobin. At that time the ferrous sulfate was increased to 0.648 Gm. three times a day and 10 units of liver extract (Lederle) were started every other day. After 50 units had been given, erythematous nodes developed about the legs and the medication was stopped.

In the latter part of October the patient spotted for four days and was put to bed. There were no cramps and the uterus appeared to be enlarging normally. Subsequent course was normal, quickening felt on Nov. 15, 1944. The red blood cells and hemoglobin continued to remain somewhat low, ranging from 3,000,000 to 3,600,000, and 56 to 63 per cent, respectively, in spite of the continued large dosage of ferrous sulfate. At the checkup examination on December 28, the patient complained of marked gastric distress, which disappeared when she had, of her own accord, stopped the iron. Lextron was substituted, but this too produced the distress and was shortly discontinued. The patient received no further iron for the remainder of the pregnancy.

On Jan. 28, 1945, the patient complained of marked listlessness. Check-up examination was normal except for a red blood count of 2,890,000 and hemoglobin of 53 per cent. In view of the iron and liver extract intolerance, it was decided to transfuse her. This was done without incident with 500 c.c. of citrated blood, on Feb. 8, 1945, following which the patient felt considerably improved.

Lightening occurred somewhat early, on February 23, the patient experiencing mild pressure symptoms, and moderate hemorrhoids, which persisted throughout the remainder of the pregnancy. On March 10, she complained of marked malaise, listlessness, and anorexia. General examination was negative except for a mild temperature elevation (99.6° F. at 2 P.M.), and two moderate-sized hemorrhoids. The pregnancy was enlarging normally, fetal heart 136 in the lower left quadrant, and the head below spine by rectal examination. Urine was negative. Blood count was within normal limits, the transfusion having elevated the red blood cells to 4,100,000. No cause for the slight temperature elevation was discernible.

The patient continued to complain of marked malaise and anorexia and became definitely depressed mentally. She was seen frequently, in view of the abnormal course so close to term (April 3, 1945). She stated that it was a marked effort for her to get out of bed. She continued to run an evening temperature elevation, usually to about 100° F., and, on occasion, to 101° F. at night followed by a marked night sweat. Chest x-ray was

TABLE I. MATERNAL BLOOD COUNTS

	9/5	10/6	11/6	12/4	12/28	1/28	3/10	3/22	3/26	3/29	3/31	4/2	4/9	4/14	4/21	4/28	5/5	5/26	6/26
R.B.C.	3.87	3.32	3.21	3.44	3.08	2.89	4.10	3.92	3.78		3.87	3.67		3.87	4.01	4.06	4.01	4.13	4.20
Hgb. (%)	70	62	61	60	59	53	71	72	66		67	67		68	72	72	73	75	76
W.B.C.							9,050	8,850	12,700		11,800	15,500		9,450	8,850	9,450	6,550	7,550	8,600
Segs.							70	71	54		33	20		31	36	36	44	48	47
Band.										DELIVERY		2							
Lymph.							25	26	40		60	70		63	60	59	51	47	52
Eos.							3		1			1		1		1	1		
Basos.							2							5	4	4	4	5	1
Mones.								3	5		7	6	Neg.						
Heterophile								Neg.					Pos.						

TABLE II. INFANT BLOOD COUNTS

	4/6	5/1	5/4	5/12	5/16	5/19	5/26	6/2	6/9	6/16	6/26	7/3
R.B.C.	4.31	1.92		3.56	3.00	3.09	2.75	3.22	3.15	2.98	3.32	3.36
Hgb. (%)	85	30		60	51	52	47	53	53	49	57	63
W.B.C.	10,600	6,300	TRANSFUSION	6,300	6,500	7,200	7,950	7,500	8,750	6,200	7,050	6,250
Segs.	54	20		19	18	19	23	25	15	20	24	26
Lymph.	39	71		77	79	75	73	71	81	77	72	70
Mones.	6	7		4	3	4	3	3	4	2	4	3
Eos.	1	2		0	0	2	1	1	0	1	0	1

negative on March 22. Physical examination continued negative; the fetus enlarging. Red blood count at this time was 3,920,000; hemoglobin 72 per cent; white blood count 8,850, with segmented cells 71 per cent; lymphocytes 26 per cent; monocytes 3 per cent. Agglutination reactions for typhoid, typhus, and melitensis were negative. Heterophile agglutination was negative. On March 26, a differential smear revealed a rather marked change in the poly-lymph distribution, 54 per cent and 40 per cent, respectively, so that infectious mononucleosis was suspected.

On March 28, in view of the extreme debility of the patient, continuation of fever, absence of a positive diagnosis, and concern for the fetus, it was determined that labor should be initiated by rupture of the membranes. This was done at 8 P.M. Labor began at 10 P.M., and at 1:30 A.M. on March 29, a 4-pound 13-ounce female infant was delivered in the left occipitoanterior position with outlet forceps. The child cried spontaneously.

In all, the patient was in hard labor for three hours, normally delivered, with a normal third stage. On March 31, 1945, four days post partum, the diagnosis was tentatively established as infectious mononucleosis, the blood count revealing a continuing change in the normal white cell proportion:

Red blood cells, 3,870,000
Hemoglobin, 67 per cent

White blood cells, 18,750
Segmented cells, 63 per cent
Lymphocytes, 60.5 per cent
Monocytes, 6.5 per cent

However, on this same date the heterophile antibody reaction, as well as the typhus, typhoid, and melitensis, remained negative.

Postpartum course was normal except for a continued evening temperature rise of 99.6° or 100° F. Debility was marked for the first three days but then began to disappear rapidly. Appetite developed for the first time in weeks. On April 2 the white cell disproportion had become even more marked: polys 20.5 per cent, and lymphocytes 70 per cent. On April 9 the diagnosis was finally established by positive heterophile reaction, in a dilution of 1:128. The subsequent course has been a general progressive improvement in the patient, as well as a gradual rearrangement of the white cells to the normal pattern (Table I).

As a matter of interest, a complete blood count was done on the infant on the seventh postpartum day. It revealed:

Red blood cells, 4,310,000
Hemoglobin, 85 per cent
Occasional nucleated red cell

White blood cells, 10,600
Segmented cells, 54 per cent
Lymphocytes, 39 per cent
Monocytes, 6 per cent
Eosinophiles, 1 per cent

The child, weighing 4 pounds, 13 ounces, at birth, was considered premature. She was placed on a weak evaporated milk formula, given subcutaneous fluids twice daily, and kept warm. Progress was normal and weight was 6 pounds, 3 ounces, at the first month. At this time and for several days prior, it was noticed that although the child cried and ate well there was a progressive pallor and waxiness. A surprising red count was found on May 1, 1945:

Red blood cells, 1,920,000
Hemoglobin, 30 per cent

White blood cells, 6,300
Segmented cells, 20 per cent
Lymphocytes, 71 per cent
Monocytes, 7 per cent
Eosinophiles, 2 per cent

In spite of the fact that the child was then a month old, concern was felt regarding the Rh factor. The mother and father proved to be Rh positive and the infant Rh negative. On May 3 the child was transfused with 150 c.c. of Rh-negative blood, given in the bone marrow of both tibiae. There was an immediate improvement in the count and general appearance. Red blood count was 3,560,000, with 60 per cent hemoglobin on May 12. However, four days

later the count had dropped to 3,000,000 with 51 per cent hemoglobin. Physical examination of the infant was normal. She was gaining well, cried lustily, and nursed well. The spleen was not palpable. It was thought advisable to start 2 grains of ferrous sulfate daily by mouth.

The count remained about the same until May 26, at which time it dropped to 2,750,000, with 47 per cent hemoglobin. During this time the white blood cells remained within limits of 6,000 to 8,000 with about a 70 per cent lymphocyte and a 20 per cent segmented cell proportion. This was considered to be within normal limits for an infant. At this time, the infant began to have a dietary upset, thought possibly to be due to forcing iron by mouth, so that a change was made to intramuscular injection of iron cacodylate, $\frac{1}{4}$ grain every second day, and, in addition, 0.33 c.c. reticulogen every third day. Under this management the count continued to remain at about 3,000,000 with 50 to 53 per cent hemoglobin until June 16. At that time the spleen became palpable about 1 fingerbreadth below the left costal border. The dietary upset had disappeared with the discontinuation of iron by mouth and the child appeared to be doing well, weighing 9 pounds, 2 ounces (2 $\frac{1}{2}$ months old). Since we seemed to be getting nowhere with rather large amounts of iron and liver extract, it was decided that all medication should be stopped. Strangely enough, the red blood count rose to 3,860,000 with 60 per cent hemoglobin within two weeks, and splenic enlargement disappeared. At three months the child weighed 10 pounds, 12 ounces, and concern for the anemia was dropped.

In retrospect, the case has been of considerable interest from several standpoints. Symptoms and findings of mononucleosis in the mother were somewhat different from the usual picture. We were particularly impressed with the extreme debility and mental depression, in a usually happy and vivacious personality. There was an absence of previous throat infection and no glandular enlargement. The rather high evening temperatures and particularly the night sweats complicated our consideration of the problem.

Obviously, in so far as anemia in the child is concerned, no conclusions can be reached. It appears that the Rh factor was not important. It could well have been an iron deficiency anemia, since the mother had had no iron for three months and had eaten very little for five weeks prior to the delivery. Whether or not mononucleosis in the mother was influential in the child's anemia remains to be proved.

I wish to acknowledge the assistance of Lt. Helen R. Cash, WAVE technician, whose accurate laboratory work made this article possible.

USE OF CURARE TO RELIEVE DYSMENORRHEA

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THIS clinical report is based on the use of curare* by injections on 73 occasions to 49 women, who were suffering from dysmenorrhea believed to be of primary type.

The observation that curare might be of assistance in the treatment of dysmenorrhea came about in the following manner: The literature on curare contains the report of Bennett and Cash¹ on the use of a very small dose of curare as a diagnostic test for myasthenia gravis. The test is based on the action of curare, interruption of the nerve impulse at the myoneural junction, causing brief weakness of voluntary muscles resembling the clinical picture of myasthenia gravis. The injection of one-tenth of the physiologic dose of curare will so exaggerate the weakness in a patient with myasthenia gravis as to confirm the diagnosis.

In December, 1943, I applied this test in the case of a young woman suspected of having myasthenia gravis. Prostigmine methylsulfate and atropine were at hand to terminate the added muscle weakness in case the small dose of curare should cause any severe reaction.

Intravenous injection of 50 units of purified curare caused transient lid droop and double vision but no embarrassment of respiration. An additional 50 units revealed no general muscular paralysis, so I felt that myasthenia gravis was ruled out. In a few minutes the patient arose stating, "You can use that stuff on me again, my cramps are gone!"

The possibility that minute doses of curare would influence menstrual cramps was then considered.

Shortly after this a nurse asked for help for severe menstrual pain. I administered 70 units of intocostin in one dose, intravenously. She experienced immediate relief, returned to duty and had no return of discomfort.

After repeating the successful experiment on the nurse and the original patient, I reported the facts to Dr. Stuart Cullen. Dr. Cullen² had reported a large series of cases of the successful use of curare to obtain muscular relaxation in anesthetized patients without producing deep anesthesia. Dr. Cullen was intrigued by my observations because curare is believed to have no action on involuntary musculature. We agreed that we would test the effect of curare on dysmenorrhea further. He suggested to Dr. May Danielson, then a member of his anesthesia staff, that she treat University Hospital personnel whenever the occasion arose and report the results.

Dr. Cullen and Dr. Danielson have kindly given me their data for publication with my own. The Cedar Rapids series comprises the treatment of 23 women in 34 menstrual periods, and the Iowa City series, 26 women in 39 menses.

Our results were about the same. Good results were obtained in 50 per cent of the cases. By good results I mean that the patients were able to return to work immediately or within twenty to thirty minutes and to continue at their normal activities with little or no discomfort. Another group have temporary or partial relief of pain so that results are only fair. In one third of the cases there was no relief of disability or such short relief as to make the use of curare impractical.

The necessity for parenteral administration of curare limits its usefulness. Within one minute after intravenous injection of curare the patient observes heaviness of the eye-

Two purified preparations of curare were used in these two series: Intocostin (Squibb) and d-tubocurarine chloride (Squibb).

*The materials used in this study were furnished by E. R. Squibb & Sons.

lids and often diplopia, or fuzzy vision. These effects pass in five to ten minutes. The relief experienced is immediate, coming on within two to fifteen minutes after the intravenous injection of 50 to 100 mg. of curare. A second dose of 50 mg. has been given in some instances, several hours after the initial dose. The disabilities relieved comprise cramps, nausea, headache, dizziness, and a feeling of tension.

One patient experienced dizziness lasting a half hour after the injection and fainted when she got to her feet. She was of very slight build and had received 100 mg. as an initial dose. Another time I would give such a patient a smaller initial dose.

The frequency of occurrence of dysmenorrhea has been the subject of many investigations. Any subjective complaint cannot be mathematically evaluated. Novak³ quotes M. Hodge as an authority that 5.3 per cent of 974 apparently healthy girls had such severe dysmenorrhea as to prompt rest in bed. Winther⁴ found 20.6 per cent of 7,379 University of Minnesota women students had discomfort sufficient to necessitate going to bed.

Dysmenorrhea, including menstrual pelvic pains, headache, leg ache, nausea and vomiting, and tension must represent a considerable loss of time in industry. Prompt and safe therapy which contributes to the relief of suffering and lessens hours lost from normal occupation is of importance.

It is interesting to speculate on the *modus operandi* of the relief of menstrual pain experienced with the injection of curare. The drug may improve the circulation to the uterine muscles by its relaxing action on all skeletal musculature. Bickers⁵ believes the pain of dysmenorrhea is comparable with that of angina pectoris and other painful muscular contractions caused by insufficient oxygenation of the contracting muscles.

With one patient being investigated between menses for sterility by hystrogram when cramping was severe after the filling of the uterus with iodized oil, a roentgenogram was made, then 100 units of curare were injected intravenously. Within two minutes of the injection, pain was less, and a second film was taken at the same distance and angle. The two films superimposed almost exactly. Probably the relief of pain was owing to the escape of the iodized oil through the open ends of the tubes and not to any relaxation of the uterus.

The need of an intravenous or intramuscular injection which may have to be repeated after four hours is the chief drawback to the convenient use of curare for the relief of dysmenorrhea. Small doses are harmless unless the patient should have myasthenia gravis. In this event the effect of the curare would exaggerate the muscular weakness and might temporarily embarrass respiration. This could be offset at once by a dose of prostigmine.

Curare does not upset glandular function as do so many of the endocrine preparations used for the treatment of dysmenorrhea. Extracts of curare are inexpensive. Another advantage of curare is that it acts instantly. The various aspirin compounds so extensively used to cover up menstrual pain cause nausea, sweating, and weakness in many instances. Curare does not have these drawbacks.

Furthermore, curare is not habit forming as are opiates, too often administered as a last resort. The repeated use of curare has appeared to be followed by less severe pain at subsequent periods, doubtless a psychological effect.

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EARLY CLINICAL AND ROENTGENOLOGIC DIAGNOSIS OF ANENCEPHALY

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THE importance of early diagnosis in fetal monstrosities cannot be too greatly stressed, as it precludes the possibility of unwittingly allowing the patient thus burdened to progress to term. To the present time, however, review of reported cases of anencephaly, considered the most common type of monstrosity, shows that those diagnosed before delivery and definitely confirmed by x-ray are very few in number. This is true even in instances where prenatal care was instituted as early as the second or third month of pregnancy. It was found, too, that in those diagnosed, suspicion of defect was generally not initiated until about the seventh month of gestation, at which time there usually was a rapid uterine enlargement because of hydramnios.

Associated with this increase in amniotic fluid very frequently is an indistinct or absent fetal heart tone; however, this diagnostic feature is thought to be due also, in part, to the fact that "the cardiac muscle, although physiologically formed and sufficiently nourished, is lacking in innervation for its function because the cerebral and even spinal centers may not be developed" (Gigli).

Accompanying the uncertain heart tones may be a subjective and palpatory lack of fetal movement. When elicited, it is of the exaggerated spasmodic or convulsive type and may partially account for complaints of abdominal pain by the patient, which, it seems, are present more often than in the normally pregnant woman.

Also, with obscurity of outline of the fetal skeleton or faulty outline of the presenting part, the possibility of abnormality must be entertained.

With these facts before us, we submit the following case:

L. E., a 27-year-old, unmarried, white girl presented herself for examination complaining of occasional dull abdominal pain of recent origin. Inspection and palpation of the part on April 3, 1945, revealed a symmetrical, tense, cystic mass filling the lower abdomen and extending to the umbilicus.

Although history of exposure to pregnancy was elicited, and last menstrual period admittedly was early in October, 1944, with abdominal palpation no ballottement was noted and no fetal parts could be definitely outlined. No fetal heart tones nor uterine souffle could be heard, and no fetal movements were felt. Subjective fetal movement had been denied to the time of initial palpation; infrequent spasmodic movements were noted thereafter. Breasts were tense with slightly enlarged areolae and prominent Montgomery tubercles. Pelvic examination showed external genitals negative, outlet marital, marked congestion of vaginal and cervical mucous membranes to actual purplish discoloration. Cervix was normal in size and position, but presented a softened tip. Fundus was felt to be enlarged and soft. Adnexa were negative. The remainder of the physical examination was also negative.

Since the presumptive signs of pregnancy were so clearly defined, but presence of a normal fetus was questionable, it was felt that x-ray was indicated to confirm the probability of a fetal abnormality. Diagnosis of an anencephalic monster was established by this method, as roentgenogram on April 4, 1945, showed a single fetus of approximately four to four and one-half months development, whose skull formation was replaced by two small ossified knobs. The uterine shadow was well outlined and was larger than expected with a fetus of this size corroborating the impression of hydramnios. Repeat films several days later verified the diagnosis of anencephaly with hydramnios and showed surprising increase in the uterine size.

The patient was referred for hospitalization on April 10, 1945, and the following summary received:

Prenatal course continued uneventful except for a gradual increase over normal in amniotic fluid; no fetal heart tones were heard although occasional movement was still noted by the patient. On April 22, when the uterus had increased to the size of a seventh month pregnancy, fetal movements ceased.



Fig. 1.—Arrows point to the two calcareous knobs which replace the normal skull formation.

On April 25, membranes were ruptured and approximately 700 c.c. of fluid escaped at the time. Drainage of fluid continued the following day with a few uterine contractions. On April 27, the patient had moderately severe uterine contractions and her previously normal temperature rose to 101.3° F. with attendant rapid pulse of 128 per minute. She appeared ill and was started on penicillin, 30,000 units every two hours intramuscularly. That afternoon vaginal examination revealed cervical dilatation of 1 to 2 cm. and during examination the left arm prolapsed. Under sodium pentothal anesthesia, the cervix was further dilated to 3 to 4 cm. and the other arm prolapsed during this procedure. After dilatation, the macerated anencephalic fetus was extracted with some difficulty. Placenta and membranes were expressed complete. Immediate condition of the patient was good. Two days later penicillin was discontinued and her convalescence progressed satisfactorily.

Gross pathologic examination of the specimen revealed a fetus with a crown rump length of fifteen centimeters, about four and one-half months gestation, the cord and placenta at-

taehed. Outstanding features of the fetus were replacement of the calvarium by a sac of edematous fluid which had been ruptured, and ascites which distended the abdominal wall to a thin membrane. The eyes were bulging and the forehead receded. The tongue and lower jaw were torn in delivery and revealed a fused hard palate. The spinal column was not fused. External genitals were of the female type. The brain was represented only by dilated nervous tissue over the expanded ventricles. The bones of the calvarium were missing and the skull was formed by the fused sphenoids which protruded backward from the spine. The spinal cord was exposed and the neural arches of the vertebrae extended laterally instead of posteriorly and were flattened over the center of the vertebral column. On sectioning, the liver was flabby and torn. The intestinal tract had a gangrenous, infected appearance. Heart was normal in appearance. Because of maceration throughout, no sections were made.

TABLE I

AUTHOR	GRAVIDA	SIGNS OR SYMPTOMS SUGGESTING X-RAY	FETAL HEART	DURATION OF PREGNANCY (WEEKS)
Case, J. T.	iv	Hydramnios; no fetal movements	No	28
Case & Cooper	iv	Hydramnios	Yes	32
	iv	Hydramnios	?	32
	iv	Hydramnios; prenatal care from 3 months	Yes	28
Tracy, F. E.	i	Hydramnios	Faint	32
	i	Hydramnios; prenatal care from 2 months	No	30
Jennings, C. H.	iii	1 wk. overdue; abnormal presenting part; prenatal care from 3 months	Until 48 hrs. before delivery	43
Harris, A. T.	vi	Hydramnios	?	40
Doub, H. P.	i	Hydramnios	Yes	30
	i	Hydramnios	?	36
Maier, R. J.	i	3 weeks overdue	Yes	43
	i	Hydramnios	No	30
Spangler, D.	?	Hydramnios	?	36
	iii	Toxemia	No	34
Winn, et al.	i	Toxemia; hydramnios patient a diabetic	No	26
	v	Hydramnios	No	28
	iv	Hydramnios	No	40
Lloyd	?	Question of pregnancy; no subjective fetal movement	?	33

Discussion

Several salient features of the above case demand attention, first and most important of which we consider to be the early diagnosis. According to menstrual history at the time of initial examination, the pregnancy should have been about 25 weeks in progress. However, palpation found the upper uterine boundary not to exceed the level of the umbilicus. It is recognized that an anencephaly fetal growth is stunted, particularly in the early months of pregnancy. Body measurements of various parts are less than in the normal fetus for the same period of development. On this basis we shall assume that the dates of history approximate the correct, even though the gross pathologic report describes the fetus as of four and one-half to five months' development.

Recognizing the fact that the fetal skeleton in its entirety cannot be well visualized by roentgen ray until about the eighteenth week, it is felt that this represents one of the earliest cases diagnosed clinically and confirmed by x-ray. Radiographic absence of a skull shadow alone was not used as a criterion for diagnosis as that is of no great significance; a rapid fetal movement will obliterate that shadow, particularly if the exposure is over one second. However, the replacement of the skull shadow by two small round ossified knobs (sphenoids)

is quite characteristic of the anencephalic development. In an older fetus, even the facial bones may be distinctly seen crowned by the small knobs described.

Another feature of this case to be mentioned was the presence of an almost complete spina bifida which in some degree usually accompanies anencephaly. Occasionally this deformity can be diagnosed from the abdominal film, particularly if the defect is very large and the rib ends are considerably separated from the vertebral bodies.

Initial palpation of the uterus revealed no appreciable hydramnios. However, in the short interval of four days between x-ray films, the fluid had already increased and was clearly illustrated by comparison of the uterine outline in those films. This indicates the rapidity with which amniotic fluid is secreted in abnormal pregnancies.

Since 1916, at which time diagnosis of fetal monstrosity was first substantiated by x-ray, approximately only eighteen cases have been reported with confirmation by x-ray. Résumé of these cases is charted in Table I.

Of special interest on the above chart are the three cases which had prenatal care instituted in the second or third month. Also to be noted are the two instances in which the patients progressed three to four weeks beyond the expected date of confinement.

Parity of the patient seemed not to influence the occurrence of the monstrosity, as it was well divided apparently between primiparae and multiparae. Although not specifically shown here, the maternal age group was also deemed nonrelated to incidence. Hydramnios was the predominant cause for suspecting abnormality and suggested the wisdom of check x-ray. As has been mentioned, hydramnios was usually around seven to eight months in appearing. The above chart also concurs with the fact that the fetal heart tones are frequently not heard, or, if present, are likely to be weak.

It is felt that discussion of the case would not be complete without mention of the fact that details of delivery were not accorded the patient to circumvent the possibility of exciting a psychosis with future pregnancies.

Summary

A case of anencephaly has been reported in which clinical and roentgenologic diagnosis was made relatively early in fetal life. With modern technique, a simple anterior-posterior film of the pelvis early in pregnancy is fraught with absolutely no danger to the mother or fetus. Therefore, in cases of questionable diagnosis this facility for clarifying it should be readily used. It is felt that diagnosis of abnormalities of this type with subsequent therapeutic abortion is of obstetric as well as psychological value.

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ARGENTAFFIN CARCINOMA (CARCINOID TUMOR) ARISING IN AN OVARIAN DERMOID CYST*

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IN 1939, Stewart, Willis, and de Saram¹ observed for the first time the occurrence of carcinoid tumors arising in connection with ovarian dermoid cysts. In their first case, because of inadequate material for study, these authors were unable to find the intestinal tissue of origin, but, in their second example, they clearly demonstrated that the tumor arose from epithelium of the type found lining the normal ileum. Of noteworthy interest was the fact that, although this intestinal tissue did not form a complete segment of gut, strands of "muscularis" were present, and these strands were markedly hypertrophied in zones which were infiltrated by tumor. This phenomenon of myohypertrophy had been previously described in cases of carcinoid tumor involving different segments of gastrointestinal tract, but it had always been ascribed to the effects of intestinal obstruction and not to any direct action on the part of the tumor cells.

In recording the third case of this pathologic curiosity Gabilove² was able to identify a diminutive segment of gastrointestinal tract including a portion which appeared histologically to be lined by gastric mucosa. In this mucosa numerous nodules of carcinoid tumor were found. His case was the only one of its kind from the standpoint of a "dermoid" origin, and the fourteenth recorded instance of carcinoid tumor arising in gastric mucosa.

While studying a large series of dermoid cysts we encountered, more or less accidentally, a very small nodule of argentaffin carcinoma (carcinoid tumor) in an ovarian cyst. The following is a brief report of our case.

Report of Case

A white woman, 59 years of age, came to the Mayo Clinic on May 2, 1938, complaining of constant suprapubic pain of eight days' duration. For one year prior to this episode she had had a dull intermittent aching pain in the right lower portion of the abdomen. For a similar period she had suffered from mild nocturia. Her menstrual history had been normal and the menopause, which she had experienced at the age of 53 years, had been uneventful. She had had one child.

Positive physical findings were limited for the most part to the examination of the pelvis, which revealed bilateral masses the size of a grapefruit, which were believed to be cystic, and considered as being probably ovarian in origin.

At operation, through a low midline abdominal incision, bilateral ovarian dermoid cysts were found. The uterus contained multiple small fibromyomas. Hysterectomy with bilateral salpingo-oophorectomy and appendectomy were performed.

From the standpoint of our report, the ovarian "dermoids" furnished the main points of interest. Each was approximately 8 cm. in diameter, unilocular, and almost completely cystic. The content of sebaceous material, hair, and so forth, was that which one usually expects, and the small "dermoid processes" were not remarkable grossly. Blocks of tissue

*In deference to common usage, the term "dermoid cyst" is herein used instead of the more accurate designation "cystic teratoma."

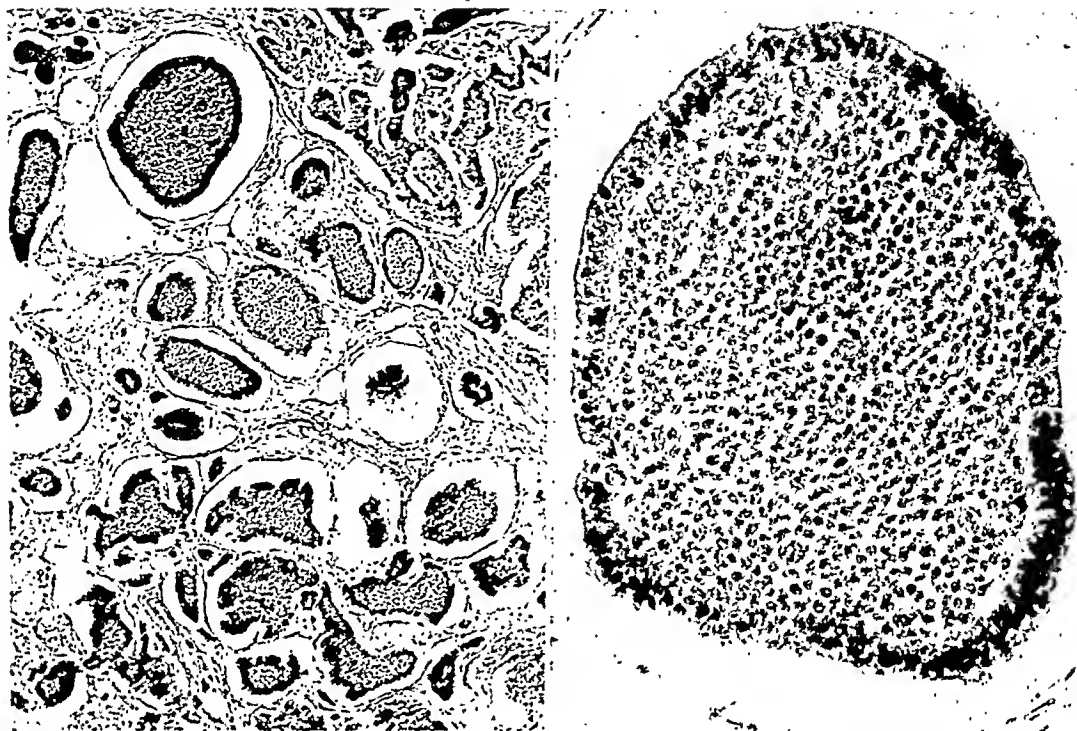


Fig. 1.—Details of a cellular island of tumor tissue illustrating the phenomenon of peripheral palisading of cells (hematoxylin and eosin).

Fig. 2.—Argentaffin carcinoma (carcinoid tumor) occurring within a dermoid cyst. The cells are small and hyperchromatic and are disposed in islands and strands which appear separated by tissue clefts from the surrounding stroma (hematoxylin and eosin).

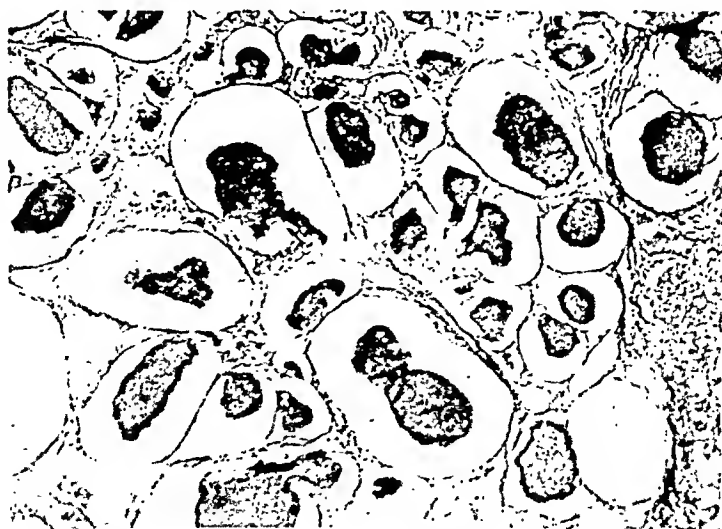


Fig. 3.—The argentaffin character of the cells is seen with a blackening of the cytoplasmic granules (silver impregnation method).

sectioned and stained in the usual way revealed squamous epithelium, eccrine and apocrine sweat glands, sebaceous glands, and hair follicles. In addition, isolated patches of brain tissue, bone, smooth muscle, adipose connective tissue, bronchial epithelium, and peribronchial mucous glands were encountered. In one of the blocks routinely selected from the left ovarian tumor a microscopic-sized portion disclosed, with hematoxylin and eosin preparations, an appearance which at once suggested the diagnosis of carcinoid tumor (Fig. 1). The cells were small, prismatic in shape, dark-staining and granular, and were arranged in islands and strands which exhibited a degree of palisading of the peripheral layers (Fig. 2). Comparing the appearance of the tumor with that of a large group of ileal carcinoids (reported elsewhere by one of us [Dockerty] and Ashburn³) it was evident that our diagnostic impression was a certainty. Preparations on other blocks, using silver impregnation methods, confirmed our findings, the cytoplasm of the tumor cells showing numerous argentaffin granulations (Fig. 3). Search was then carried out on remaining portions of the block and on adjacent tissue subsequently taken from the original tumor in an effort to establish the identity of the gastrointestinal tissue of origin. Our attempts were unsuccessful and, accordingly, we were left to assume that the neoplastic process had begun in a small group of cells rather than in a macroscopic segment of intestine as found by Gabrilove. Since we have not found any reports other than the afore-mentioned, we are accordingly submitting our case as representing the fourth example of argentaffin carcinoma (carcinoid) occurring within a dermoid cyst.

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RECURRENT PLACENTA PREVIA AND THE SIGNIFICANCE OF PLACENTOGRAPHY AS A DIAGNOSTIC CRITERION

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WITH an incidence of placenta previa at the Boston Lying-In Hospital of 1.92,¹ one would expect a reasonable number of such patients to repeat their experiences. However, a search of case histories at this hospital shows that this complication recurred only in two patients since 1925. A review of the literature reveals only ten cases of recurrent placenta previa in successive pregnancies,^{2, 7} and one case in nonsuccessive pregnancies.⁸ The scarcity of cited instances of recurrent placenta previas cannot be ascribed to the failure of obstetricians to report these cases but, more likely, to the fact that placenta previa recurs only rarely, as demonstrated in our statistics. Fried and Torpin⁷ report the most recent case of recurrent placenta previa in successive pregnancies since 1931. Vaginal examinations did not establish conclusive evidence of placenta previa in either pregnancy. Concerning the patient's first pregnancy, they say: "No placental tissue was felt at the os, which was found to be dilated 3 cm. and slightly effaced." Vaginal examination in the subsequent pregnancy "failed to reveal placental tissue near the cervical os, which was found to be dilated 2 cm. and uneffaced." On each occasion the patient was delivered uneventfully via the pelvic route.

It is the purpose of this report to present two cases of recurrent placenta previa, one, in nonconsecutive pregnancies, and the other, in consecutive pregnancies.

CASE 1.—Mrs. C., a 25-year-old primipara, due March 2, 1940. She was admitted to the hospital on Feb. 19, 1940, for evaluation of painless vaginal bleeding. Twelve hours prior to admission she passed about three teaspoonfuls of bright red blood with several small clots. Palpation of the abdomen showed the vertex to be floating high over the inlet. Cystograms and soft tissue films showed evidence of placenta previa, because the placenta was visualized low on the posterior uterine wall. These findings were immediately corroborated by vaginal examination, performed in an operating room prepared for an immediate abdominal section. Placental tissue was palpated 1 cm. from the internal os on the posterior uterine wall, extending to the left lateral wall. Since moderately brisk bleeding resulted from this examination, a rapid classical cesarean section was performed, and an active 7-pound, 9-ounce male infant was delivered. At operation, the placenta was readily identified on the left posterior aspect of the lower uterine segment, extending within 1 cm. of the internal os. Diagnosis: marginal placenta previa.

In her second pregnancy, Mrs. C., due Feb. 17, 1941, was admitted to the hospital on Jan. 29, 1941, for evaluation of painless vaginal bleeding (approximately 8 c.c.). Placentography revealed the placenta again attached to the posterior uterine wall with the greatest thickness at the equator of the uterus. The vertex was floating over the inlet. Since there was no vaginal bleeding after five days of hospitalization, she was discharged. It was decided that she should be admitted on the due date to await pelvic delivery. On February 26, the patient was delivered uneventfully, by low forceps, of an

8-pound, 14-ounce female infant. Exploration of the previous section scar showed it to be intact.

In her third pregnancy, Mrs. C was due Nov. 25, 1943. Abdominal palpation on October 13 revealed the vertex floating high over the inlet. Since there was a question of hydrocephalus, a lateral film of the uterus was taken. The vertex was found to be normal, but the placenta was visualized low on the posterior wall, consistent with the diagnosis of partial or complete placenta previa. A flat plate of the abdomen showed the fetal head displaced toward the right iliac fossa. It was evident that the patient had a greater degree of placenta previa in this pregnancy than in her primiparous one. Therefore, an elective repeat cesarean section was scheduled one week from term. The patient was admitted to the hospital on Nov. 18, 1943. A severe upper respiratory infection necessitated postponement of the operation. However, 36 hours after admission, the patient passed several small dark elots. Therefore, on Nov. 20, 1943, the patient was delivered by means of a Krönig cesarean section of an active 8-pound, 11-ounce male infant. The placenta was found low on the posterior uterine wall, completely covering the internal os. Diagnosis: complete placenta previa.

CASE 2.—Mrs. M. R., was a 40-year-old para vii, due Oct. 16, 1942. The past obstetric history revealed that the patient had been delivered five times normally and once by breech extraction. The fifth pregnancy resulted in a stillborn infant because of premature separation of a normally implanted placenta.

The patient was admitted to the hospital with her seventh pregnancy at 12:30 A.M. on Sept. 26, 1942, because of bright red vaginal bleeding (approximately 6 to 8 c.c.). Previously there had been a small amount of vaginal bleeding at the third and sixth months. The blood pressure on admission was 124/76, the pulse rate 80, and the patient's condition was good. Examination of the abdomen revealed the vertex floating over the inlet. The infant lay in the right occipitoposterior position. The fetal heart was heard in the right lower quadrant at the rate of 132 beats per minute. Soft tissue films, taken shortly after admission, showed the placenta to be attached low on the anterior uterine wall, consistent with a marginal placenta previa. In view of these findings, immediate vaginal examination was made under "double set-up" precautions. The cervix was soft, not effaced, and dilated 3 cm. The placenta was palpated on the anterior wall of the lower segment and extended within 2 cm. of the internal os. Since the patient began to bleed briskly, a classical cesarean section was performed immediately. An active 6-pound, 7-ounce female infant was extracted by the vertex. The post-operative course was uneventful. Diagnosis: marginal placenta previa.

The patient, as a para viii, registered for prenatal care on Nov. 27, 1943. The expected date of confinement was Feb. 16, 1944. However, on Feb. 6, 1944, she was admitted to the hospital because of painless vaginal bleeding (8 to 12 c.c.) which began one and one-half hours prior to admission. The blood pressure was 128/66, the pulse rate, 96. Abdominal palpation revealed the vertex to be floating high above the inlet. The infant was in the left occipitoposterior position with the fetal heart rate 144, located in the left lower quadrant. Soft tissue films, taken shortly after admission, showed the placenta to be implanted extremely low on the anterior uterine wall. These findings were indicative of a complete placenta previa. Therefore, with the operating room in readiness for an immediate section, a sterile vaginal examination was made. Palpated placental tissue, covering the internal os, confirmed the diagnosis of complete previa. Accordingly, a classical cesarean section was performed. An active 7-pound, 3-ounce male infant was delivered by the vertex. At operation, the placenta was found covering completely the internal os. Diagnosis: complete placenta previa.

Comment

Recurrent placenta previa as an entity per se is an uncommon obstetric complication as shown by the scarcity of cases observed in our clinic and the relatively few cases reported in the literature. This phenomenon is difficult to explain. Since placenta previa is chiefly a multiparous complication, multiparity, together with faulty decidua, undoubtedly is the most important etiological factor.

The reason for allowing a pelvic delivery in Case 1 with the second pregnancy may be questioned by some obstetricians. When a previous cesarean section has been done for a temporary indication, it is the policy of this clinic to allow the patient to have a test of labor under close observation. These patients are delivered by low forceps shortly after full dilatation, with immediate exploration of the uterine scar. This procedure has been pursued several hundred times without the occurrence of a single ruptured uterus. Patients who were febrile in the puerperium following the original section are never given a test of labor.

The advent of placentography invaluablely facilitates an early diagnosis of placenta previa. We feel that a more accurate interpretation of soft tissue films can be made by application of the following criteria.

1. If the placenta cannot be visualized upon the anterior or posterior uterine walls, a diagnosis of complete previa should be made and confirmed by vaginal examination.

2. When the maximum thickness of the placenta is visualized at or below the equator of the uterus on the anterior uterine wall, it is very likely to be a placenta previa. The likelihood of a complete previa increases proportionately with the distance of the maximum thickness of the placenta below the equator of the uterus.

3. When the placenta is visualized low on the posterior uterine wall, displacing the presenting part three or more centimeters from the tip of the sacral promontory or from the base of the fifth lumbar vertebra, a diagnosis of placenta previa should be accepted and corroborated by vaginal examination.

Brown and Dippel⁹ noted that calculation of the distance between the presenting part and the sacral promontory was a valuable aid in the diagnosis of placenta previa for the posterior wall implantations, but no figure of mensuration was given.

In this clinic, soft tissue films are taken on all patients who have experienced vaginal bleeding during the last trimester. An exception is made only in those patients suffering shock from massive vaginal hemorrhage. Often, when the placenta is visualized high in the fundus, routine vaginal examinations are deemed unnecessary. Conversely, when the placenta is perceived below the equator of the uterus or not seen at all, prompt vaginal examination, for the corroboration of the diagnosis should ensue, always in an operating room prepared for an immediate section to assure safety.

Summary

1. Recurrent placenta previa is an uncommon obstetric occurrence.
2. The history of painless vaginal bleeding in the last trimester is suggestive of placenta previa, and an early diagnosis should be made with the aid of soft tissue films.
3. The skillful application of placentography undoubtedly facilitates the diagnosis of this serious complication of pregnancy.
4. Vaginal examination, under "double set-up" precautions, and cesarean section confirmed the diagnosis of recurrent placenta previa in the cases presented above.

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VESTIBULAR ABNORMAL ANUS IN A PREGNANT WOMAN

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THE vestibular abnormal anus is an anatomic phenomenon which resembles a "complete tear" of the perineum. There is present a rectovaginal spur, thick in its upper two-thirds, and becoming gradually thinner in the lower third. Control of the feces and flatus is perfect, so that whilst anatomically there is much to be desired, functionally the result is very good. In the *Revista médica municipal* of Rio de Janeiro, 1942, volume 5, page 53, De Oliveira Figueiredo reported two cases showing this interesting abnormality. In reviewing the literature he quotes Trelak, who states that the condition occurs once in every 73,000 labors. The writer recently delivered a woman who presented this abnormality.

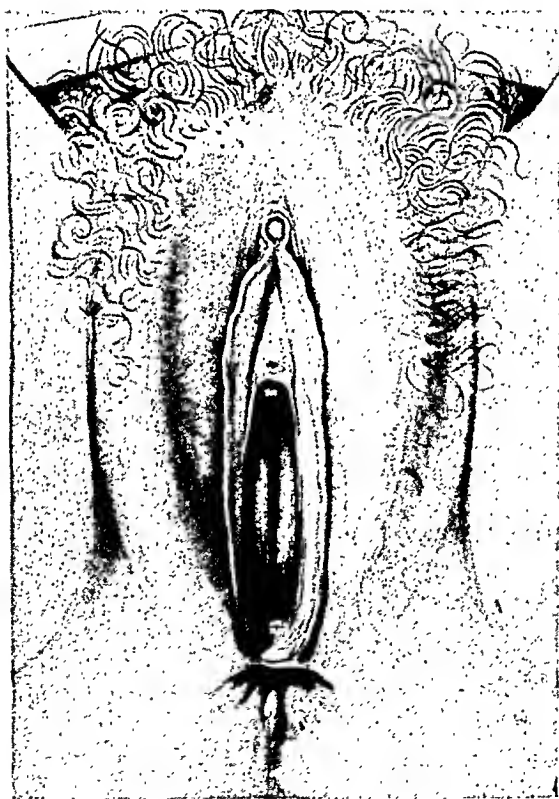


Fig. 1.

Case Report

Mrs. T., a para i, was first seen on Jan. 27, 1942. Her last menstrual period had been on November 20. The uterus was enlarged to the corresponding period of amenorrhea. Pelvic examination disclosed the following condition. There was no perineum. The labia minora were large and extended to the anal orifice where they blended with the skin around a very weak and incomplete sphincter ani muscle. The labia majora were well developed. The rectovaginal spur was very thick in its upper two-thirds. The levator ani

muscles were exceptionally well developed. The lower third of the rectovaginal septum resembled a typical "complete tear" of the perineum. The drawing (Fig. 1) depicts the phenomenon with its anatomic peculiarities. The prenatal period was normal. The labor was uneventful except for one complication—the well-developed levator ani muscle "straps" were most resistant and prevented descent of the head in the second stage. Forceps were used to complete the delivery. In order to preserve the rectovaginal septum, a wide and deep lateral episiotomy was performed. The child weighed 9 pounds, 13 ounces. The episiotomy wound was sutured immediately with chromic catgut No. 1. The total duration of labor was 48 hours. The puerperium was afebrile. Subsequent examination showed the rectovaginal septum intact, and the episiotomy wound well healed.

OPISTHOTONUS FETALIS

ALFRED J. KOBAK, M.S., M.D., CHICAGO, ILL.*

(From the Department of Obstetrics and Gynecology of the University of Illinois
College of Medicine)

EXAGGERATED deflection attitude of the fetus during parturition is rare, if the paucity of such case reports in the literature is any gauge. The following case report exemplifies such a condition:

D. A., aged 20 years, para i, gravida ii, had a normal prenatal course. She gained 35 pounds despite thyroid medication and dietary restrictions. Routine abdominal examination prior to the onset of labor failed to reveal any abnormal attitude of the fetus.



Fig. 1.

The patient was admitted to the Wesley Memorial Hospital on May 6, 1945, in labor and full term. The pains began at 10 A.M.; the first examination at the hospital revealed the presenting part to be floating. At 10 P.M. the cervical dilation was 7 cm., the membranes were intact, and the face was presenting as a mentum left transverse. However, it was diffi-

*Presented before the Chicago Gynecological Society, May 18, 1945.

cult to account for the occipital prominence and the small parts both being on the right side. Considering the possibility of some abnormality, an immediate x-ray examination was made, and the roentgenogram revealed a severe hyperextension of the fetus with both arms and legs directed to the same side as the back, the right side (Fig. 1). No skeletal anomaly was present.

A baby girl weighing 8 pounds and 4 ounces was delivered by a low cervical cesarean section at 11:45 P.M. The baby maintained a posture of extreme opisthotonus, and had difficulty in respiration. A catheter was passed into the trachea without any difficulty and no mucus was obtained upon respiration. The breathing continued as though there was some obstruction. The baby was transferred into an incubator and was supplied with oxygen. Alpha lobeline, coramine, and vitamin K were given. The prognosis was deemed to be poor. At 4 A.M. the rectal temperature was 104.2° F. The baby took liquids and soon responded favorably. The posture of the baby was still one of opisthotonus, with the arms drawn sharply back behind the arched vertebral column, bringing the scapular wings toward the midline. The care of the baby was referred to Dr. W. W. Swanson who noted that the fetus was cyanotic, but responded to oxygen. The breath sounds were harsh and dry. Breathing was through the mouth and was entirely diaphragmatic. For a while Dr. Swanson noted that the heart tones were heard best through the right side of the thorax, but later the tones were heard in the normal position. X-ray of the thorax and lumbar region showed no abnormality. The baby gradually assumed a more normal posture, but still retained the attitude of hyperextension of its torso, and the arms were drawn back dorsally, even up to its eighth day of life. The mother made an uneventful recovery and left the hospital on the eleventh day. The baby remained for further observation in the nursery, until its discharge on the fourteenth day.

This condition is rare, a similar case was reported by F. H. Falls in 1917. Here the opisthotonus of the fetus was noted with the fetus presenting transversely. Failing heart tones during labor necessitated immediate extraction. The baby never recovered from the asphyxia neonatorum. It is apparent that the fetus may not fare well either during the labor or in the neonatal period, and that there is a tendency of this posture to remain for some time following delivery. Such a newborn infant may need more than the average available oxygen to tide it over the respiratory difficulty that is present.

Reference

Falls, Frederick H.: Surg., Gynec. and Obst. 24: 65, 1917.

25 E. WASHINGTON ST.

Department of Reviews and Abstracts

Selected Abstracts

Anesthesia, Analgesia

Zecena, A., and Recinos, A.: Short Labor and Analgesia, *Obst. y ginec. latino-am.* 2: 839, 1944.

Of all the anesthetic agents and methods used for the relief of labor, the authors prefer epidural anesthesia. Their technique is as follows: 40 c.c. of a 1 per cent novocain solution are injected into the epidural space. Ten to fifteen minutes later 2 to 3 units of *pituitary extract* are injected subcutaneously. By means of this combination, not only are the labor pains diminished, but also dilatation of the cervix is hastened. Sixty patients were helped by this combined procedure without any maternal or fetal accident.

J. P. GREENHILL.

Medina, J., and Daus, J.: Peridural Anesthesia in Gynecologic Surgery, *An. brasil de ginec.* 18: 415, 1944.

The authors are enthusiastic about the use of peridural anesthesia, and they give complete details of 100 gynecologic operations which they performed under this form of anesthesia. These operations were both abdominal and vaginal and included hysterectomies, oophorectomies, uterine suspensions, appendectomies, plastic operations on the vagina, vaginal hysterectomies, vulvectomies, vesicovaginal fistulas, and amputation of the cervix. The results were excellent.

J. P. GREENHILL.

Torrie, Arthur M.: Spinal Anesthesia for Cesarean Section, *Anesthesiology* 6: 154, 1945.

The ever present question of anesthesia in obstetrics, including cesarean section, has received unusual emphasis during the past few years. Method and agent alike have been evaluated. The author relates his experience in 120 cases of cesarean section performed under spinal anesthesia. "One shot" spinal injection is the method employed. The technique is given in detail. Advantages and disadvantages are discussed. The author believes that in addition to its well-known disadvantages, "spinal anesthesia appears to have a greater and more profound effect when used in obstetrical patients than in the nonpregnant patient." It is, therefore, most important to have a competent, well-trained anesthetist in direct charge of each case, and all necessary equipment must be readily available for combating any trouble that may arise.

HARVEY B. MATTHEWS.

Mammary Glands

Brougher, John C.: Prevention and Treatment of Postpartum Fissured Nipples With Local Applications of Vitamin A and D Ointment, *West. J. Surg.* 52: 520, 1944.

Cracked or fissured nipples are a common complication of the lactating period. It is estimated that cracked nipples occur in about 20 per cent of postpartum patients. Many treatment programs have been suggested for their prevention and cure.

The author has taken advantage of the well-known, stimulating, wound effect of vitamins A and D, and employed an ointment which incorporates these two vitamins. He applied the ointment immediately after delivery to a group of 200 postpartum women, and to a second group of 200 postpartum patients he used local cleanliness without the vitamin ointment. He concluded that the incidence of fissured nipples and secondary breast abscesses was greatly reduced by the use of vitamins A and D locally.

WILLIAM BICKERS.

Sanders, John T.: Factors Influencing the Morbidity and Mortality Rates in Gynecologic Surgery, South. M. J. 38: 209, 1945.

A report is made upon 500 consecutive operations in private practice. An accurate appraisal of the cardiovascular, respiratory, urinary, hepatic, and water balance system of the patient must be made before operation. The sedimentation time is the best guide for the time of operation on patients with pelvic infection. Obesity is one of the great hazards in pelvic surgery. The anesthesia must be chosen to fit the individual patient.

Postoperative care takes into account pain relief, prostigmin for distention, frequent changing of position, and test breathing to prevent emboli, intelligent use of the catheter to prevent distention of the bladder, decompression of the stomach by nasal tube, and parenteral fluids containing vitamins A and C.

There was a case fatality rate of 0.2 per cent in this group, as compared with a fatality rate of 1.8 per cent in a group previously reported. The more generous use of intravenous fluids, whole blood and plasma transfusions, early and more frequent use of intestinal decompression, together with better preoperative care, accounts for the diminished fatality.

WILLIAM BICKERS.

Miscellaneous

Quinet, A. A.: Vaginal Cytology in Precocious Puberty, An. brasil de ginec. 9: 102, 1944.

The author studied the vaginal cells in three cases of precocious puberty. One little girl was 3 years, 7 months old, the second was 7 years, 8 months old, and the third was 4 years and 2 months old. A special nuclear pattern was observed in the cells in two of the children. This consisted of a dark dash with linear condensation of the nuclear chromatin. A comparison of these special cells, with the cytological features of the vaginal cells in women of different ages, leads the author to the conclusion that these dashes represent a peculiarity of the upper cells of the stratum spinosum.

J. P. GREENHILL.

Potter, Edith L., and Willson, J. Robert: Artificial Insemination as a Means of Preventing Erythroblastosis, J. A. M. A. 127: 458, 1945.

The authors review the clinical and immunological findings in cases of erythroblastosis fetalis. They report three cases of Rh negative children whose older siblings died of erythroblastosis. One of these Rh negative children was in a case of twins, in which the mother was Rh negative and the father was Rh positive. The Rh positive twin died of erythroblastosis. Another case was reported in which the mother gave birth to a set of twins, both being cases of erythroblastosis. Both died, and the diagnosis was confirmed at autopsy. The mother was Rh negative and the father, Rh positive. She was successfully inseminated with Rh negative semen and delivered a normal infant that did not show any evidence of erythroblastosis. This lends further evidence to support the theory of maternal immunization to the Rh factor as a cause of erythroblastosis.

WILLIAM BERMAN.

The Newborn

Gori, R. M., and Bayona, E.: *The Vaginal Contents of the Newborn: The Genital Crisis*, *Obst. y ginec. latino-am.* 2: 532, 1944.

The authors studied the secretion of the vagina in 200 newborn babies. The changes were the same in full-term and premature babies. These are as follows: during the first 3 or 4 days, there is a preponderance of cells belonging to the upper layers of the mucosa, whereas in the second week of life, there is a gradual increase of cells from the deeper layers. Some leucocytes and Döderlein bacilli may be found on the third day of life, but they are short lived because two weeks later none can be seen.

Babies who undergo genital crisis have red blood cells in the vaginal smears. In the opinion of the authors, the genital crisis is only an accentuation of a complicated process which all newborn girls undergo, and which should be called a birth crisis.

J. P. GREENHILL.

Heyworth, N. Sanford, and Shmigelsky, Irene: *Purulent Parotitis in the Newborn*, *J. Pediat.* 26: 149, 1945.

Purulent parotitis, according to the number of reported instances, has been considered a rare occurrence in the newborn.

The authors report five infants with purulent parotitis during this period. A definite routine of treatment by administration of sulfathiazole and incision of the gland when fluctuation has occurred, resulted in the recovery of all five cases.

JAMES P. MARR.

Howard, Philip J.: *Paroxysmal Tachycardia in an Infant the Fourth Day of Life. Recovery With Digitalis*, *J. Pediat.* 26: 273, 1945.

Paroxysmal tachycardia in the newborn is unusual, and differs from the disease in older children, mainly by its characteristic of persistence until cardiac failure and sometimes death follow, unless proper treatment is given. The author reports such a case, and outlines the therapy.

JAMES P. MARR.

Litchfield, H. R.: *Asphyxia Neonatorum—An Evaluation—Etiology and Treatment*, *J. Pediat.* 26: 279, 1945.

It is now generally accepted that the respiratory function is under the control of a medullary center which is activated by the carbon dioxide of the blood. Thus, when the blood carbon dioxide reaches a critical concentration, the center is stimulated and respiratory movements result with the inhalation of oxygen and the exhalation of carbon dioxide.

In asphyxia, due to the failure of the respiratory center to respond to the normal stimulus of blood carbon dioxide, there is a progressive accumulation of this gas, with a corresponding lowering of oxygen concentration. The longer the asphyxia lasts, the more serious it becomes, since the oxygen content of the blood may fall so low.

As etiological factors, the author lists excessive sedatives during labor, the anesthesia during delivery, together with trauma from abnormal presentation or difficult operative procedures.

He discusses his objections to old and worthless procedures of resuscitation, such as "slapping, swinging, and tubbing, also mouth to mouth breathing." The author mentions the little value of the Drinker respirator, inhalator, pulmotors, and resuscitators.

His object is to recommend after delivery immediate removal by suction catheter of all mucous plugs and fluid, injection into the umbilical vein of $\frac{1}{20}$ alpha-lobeline, and after respiration has begun, to follow up with pure oxygen supplied through a face mask. This is an extremely important article, and deserves to be read in full by all obstetricians.

JAMES P. MARR.

Macklin, Madge Thurlow: The Diagnosis of Rh Incompatibility. Especially by Microscopic Appearances: Its Relation to the Syndrome Formerly Diagnosed as Erythroblastosis, *J. Pediat.* 25: 533, 1944.

The author, in a most learned and comprehensive article, redefines erythroblastosis. Erythroblastosis, as originally defined, indicated the presence of large numbers of nucleated red blood cells in the fetal livers at a stage in development, when erythropoiesis should largely be absent from the liver. Erythroblastosis, so defined, was present in many conditions other than those involving incompatible Rh factors in mother and fetus, such as diabetes in the mother, anoxemia and hemorrhage in the fetus.

Hemolytic disease of the newborn, proposed by some as a more correct term than erythroblastosis, is still not specific, because hemolysis may be caused by factors other than incompatibility of the Rh factor in mother and fetus.

Rh incompatibility is suggested as the term for the disease entity caused by a reaction between Rh antigens in the fetus, and the specific antibodies in the maternal blood to combat them.

Proved Rh incompatibility can be diagnosed in the living or dead infant when different Rh factors are demonstrable in mothers and fetus, and when the antibodies against the infants' Rh positive red blood cells are found in the infants' serum.

Some of the criteria used for the diagnosis of Rh incompatibility are of value when the fetus is full term, or when the infant lives for several days. They are not of value on fetuses lost early in pregnancy. The iron test is of value in these early cases.

JAMES P. MARR.

Pregnancy, Complications, Toxemia

Lascano, J. C., and Gonzalez, Warcalde J.: Subcapsular Hemorrhage of the Liver With Peritoneal Rupture During Pregnancy, *Obst. y ginec. latino-am.* 2: 757, 1944.

Nontraumatic hemorrhages of the liver are rare. However, it is not unusual to find small suffusions of blood under the liver capsule or in the liver parenchyma during the second half of pregnancy, particularly in cases of eclampsia. Occasionally, these hemorrhages become large enough to cause rupture of the liver capsule, with hemorrhage into the peritoneal cavity and even death of the patient.

In the toxemias of pregnancy, the cause of such hemorrhages may be vascular fragility, avitaminosis, changes in the blood, and anaphylactic shock. The authors report two cases in the fifth and sixth months of pregnancy. The first patient died immediately after delivery, and autopsy revealed the antemortem correct diagnosis of rupture of the liver capsule with intraperitoneal hemorrhage. In the second case, an abortion had taken place and the patient complained of severe pain in the right hypochondrium with irradiation to the back. This patient also died, and autopsy showed the same findings as in the first case.

J. P. GREENHILL.

Erickson, Carl A.: Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart, *J. Pediat.* 25: 281, 1944.

New light has been thrown on the etiological factors involved in certain congenital malformations, by three series of cases which have been reported from Australia, in which virus infections, particularly German measles (rubella), occurring early in pregnancy seem to be definitely related to the congenital defects.

The author reports 11 cases. He points out that girls should not be allowed to pass through childhood without having had rubella. The use of convalescent serum for all women who are early in pregnancy and have not had rubella should be considered. The justification for therapeutic abortion in the infected mother should deserve attention as, Swan pointed out, 100 per cent of such babies will have serious congenital malformations.

JAMES P. MARR.

Quino, N., Nölting, D. E., and Althabe, O.: *The Future of Eclamptic Patients*, *Obst. y ginec. latino-am.* 2: 860, 1944.

An attempt was made to follow up 220 eclamptic patients, but only 19 presented themselves for a thorough study. In all of them, renal function was normal. The eye grounds were normal in all except one who showed a slight degree of vascular-sclerosis. In 11.7 per cent, chronic hypertension was present. The authors maintain that the consequences of a mild but long-lasting pre-eclampsia are far more serious than those of a short, serious pre-eclampsia or eclampsia. The important factor in the future outcome of women with chronic hypertension is the duration of the toxemia.

J. P. GREENHILL.

Steiner, Melvin D.: *Aseptic Antenatal Thrombophlebitis (Phlebothrombosis)*, *New Orleans M. & S. J.* 97: 385, 1945.

Antenatal thrombophlebitis is a rare condition in contrast to puerperal thrombophlebitis. The former is apparently a noninfectious condition in contrast to the latter.

A white primipara, 36 years of age, was first seen during an uncomplicated, afebrile abortion. Several months later she became pregnant again, and soon after experienced acute pain in the muscles of the left leg. Examination revealed tenderness and redness, but no temperature. The pain and edema subsided promptly following sympathetic lumbar block. Four months later, the same pain and edema occurred in the right leg; again there was no associated febrile reaction, and the condition was controlled by lumbar sympathetic block. The patient developed pre-eclamptic toxemia, for which labor was induced and a normal child delivered. Following delivery lymphangitis and phlebitis of the left upper extremity occurred, which was attributed to chemical irritation from infusion. Throughout all of these episodes of thrombophlebitis, the laboratory examinations cast no light upon their etiology.

A fairly complete review of the literature on aseptic antenatal thrombophlebitis is presented.

WILLIAM BICKERS.

Pearl, Clifford L.: *Cervical Pregnancy*, *West. J. Surg.* 53: 71, 1945.

The theory is advanced that a fertilized ovum, passing with unusual speed down the tube and through the uterus, may reach its proper stage of growth for imbedding just as it reaches the cervix. The reason why cervical pregnancy is not more common is to be found in the fact that cervical epithelium is not well adapted for nidation.

A case of a 40-year-old woman who consulted the author because of inability to pass her urine is reported. She was catheterized, with a small amount of vaginal bleeding following the catheterization. This was the first evidence of menstruation in two months, her usual menstrual cycle being one of 30 days. Examination revealed an enlarged cervix, which was found just inside the introitus and distended the entire vagina. Upon opening the thin shell of tissue, which was the cervix, a fetus, 1.5 cm. in length, together with its amniotic sac and placenta, was removed. One month after operation, the cervix was found to be of normal size and high in the vagina. The cervical canal was patulous.

WILLIAM BICKERS.

Dingle, Phyllis: *Prophylactic Use of Pneumoperitoneum in the Puerperium of Tuberculous Patients*, *J. Obst. & Gynaec. Brit. Emp.* 51: 499, 1944.

Treatment in 30 cases of tuberculosis is described. The patient is secured rest, food, fresh air, and hospitalization when necessary. Pneumothorax is used when indicated. The first stage of labor is made as easy and as comfortable as possible. The second stage is shortened and the strain reduced by making an episiotomy and using obstetric forceps. Pneumoperitoneum is induced within one hour after delivery using 3,000 c.c. of air or air-oxygen mixture. The amount added is gradually reduced during one month. The mother

is on bed rest and does not breast feed her infant. The pressure in the abdominal cavity after pneumoperitoneum is 10 c.e. water. Under this regime, the survey shows that these patients have not been seriously affected by their pregnancy. Out of 30 cases, two were hopeless from the start and one retrogressed. Induction of pneumoperitoneum is advocated as a prophylactic measure in these cases.

WILLIAM BERMAN.

Erskine, John P.: A Case of Acute Hydramnios Successfully Treated By Abdominal Paracentesis, J. Obst. & Gynaec. Brit. Emp. 51: 549, 1944.

The author reports a case of acute hydramnios in a 21-week pregnancy (twin). Seven pints of liquor were withdrawn using a lumbar puncture needle inserted through the abdominal wall. The needle was attached to rubber tubing to a suction pump on the water tap. Three weeks later the same procedure was carried out because of a recurrence. Four and one-half weeks after this 11 pints of fluid were withdrawn. Six weeks after this 11 pints of fluid were again withdrawn. The patient delivered uniovular twins at 36 weeks, one of which was stillborn. The puerperium was uneventful.

WILLIAM BERMAN.

Chesterman, Judson T.: Choledochus Cyst Complicating Pregnancy and the Puerperium, J. Obst. & Gynaec. Brit. Emp. 51: 512, 1944.

The etiology and the pathology are discussed. Eighty per cent of the cases recorded in the literature occurred in women. The characteristic symptoms of this condition are tumor, jaundice, and pain. Treatment varies in the different cases. Marsupialization gives uniformly bad results. Anastomosis of the cyst to the duodenum has given good results. The technique of the anastomosis is described in brief. All cases, according to the author, terminate fatally unless operated upon, and anastomosis to the duodenum is a simple and satisfactory procedure.

WILLIAM BERMAN.

Necrology

SIR COMYNS BERKELEY, prominent English obstetrician, gynecologist, and author for almost half a century, well known in the United States, where he visited on several occasions, died in London, Jan. 27, 1946, at the age of 81. Knighted in 1934 for his professional attainments, Sir Comyns was a Fellow of three Royal Colleges; he was a prolific and forceful writer, the author of numerous textbooks and treatises, and the editor for twenty years of the *Journal of Obstetrics and Gynaecology of the British Empire*. His name also is intimately associated with the growth and development of the Middlesex Hospital of London, where he served from 1903 until the time of his death. The present system of midwife practice in England owes much to his devotion and encouragement. The whole life of this eminent man was absorbed by his profession, which "he pursued with undeviating energy, courage and zest until well beyond the age of normal retirement." His American colleagues may well pay a tribute to this outstanding career of a forceful and engaging figure who, moreover, followed with great interest the course and progress of this JOURNAL, and at one time had under consideration an amalgamation of our mutual interests.

Correspondence

The Combined Method in the Treatment of Cancer of the Cervix

To the Editor:

I have read with great interest in the December (1945) issue of the JOURNAL the valuable contribution of Dr. Brooke M. Anspach, entitled "A Review of the Problem of Cancer of the Cervix," and, in view of my long association with the problem, desire to comment upon certain of his statements.

Dr. Anspach presents a very lucid and complete description of the development of the treatment of cancer of the cervix from the time of Wertheim to the present day. Among his conclusions is the following sentence: "Perhaps a combination of irradiation and operation will give better results." Dr. Anspach shows in a most convincing manner why Wertheim's operation was abandoned because of the high attendant mortality. Apparently the fact escaped his attention that Schauta and his school in Vienna endeavored to overcome these objections by the substitution of the less dangerous extended radical vaginal hysterectomy. I believe that I am the only pupil of Schauta in this country, and therefore feel impelled to call attention to the fact that the results achieved by the Schauta procedure equalled those of Wertheim and Bonney with a much lower operative mortality. This was demonstrated by a report based on one thousand cases which was read before the British Congress of Obstetrics and Gynecology and published in the *Journal of Obstetrics and Gynaecology of the British Empire* (36: No. 2, 1929). The percentage of five-year salvage was 41.7 of the operated cases as compared with 39.2 for the Wertheim, and 39.6 for the Bonney procedure.

The mortality attending the Schauta operation was 3.85 per cent, in contrast to the 16 per cent of the others. The above were the relative salvages, while the absolute five-year cures were 21.6 per cent as compared with 18.5 per cent for Wertheim, and about 22 per cent for radiation treatment (Heyman). After we at the Schauta Clinic began to treat all of our patients by a combined method of operation and radiation, our results improved remarkably. I presented our experiences in a paper published in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* (33: 332, 1932), in which the salvages of patients treated by the combined method were compared with those not radiated. There was an increase of relative cures from 72 to 92.8 per cent in the two-year group, from 61 to 72 per cent in the three-year group, from 52 to 61.8 per cent in the four-year group, and from 42 to 58.8 in the five-year postoperative group. The absolute percentage (five-year cure) of all patients was 32.

These figures confirm Anspach's opinion that a combination of operation and radiation gives better results than either operation or radiation alone, as suggested likewise by Lynch, Taussig, Morton, and Meigs. The latter's results in 47 cases with preoperative radiation and without mortalities are indeed remarkable and justify a surgical approach and the combined procedure. However, I have always believed that we should not be dogmatic and that it constituted an error to subject all cancer cases to one method of treatment. Our aim should be to adapt the method to the specific condition found in the individual case. With this elective method I have treated 580 patients with cervical cancer during the years from 1921 to 1938. Of these there were 322 women who were under observation from five to sixteen years. Of these 322 women, there were 127 living, in March, 1938, which means a permanent salvage of 39.4 per cent. When we compare this with the average results in the world statistics of operated cases without radiation (about 19 per cent, with a peak of 25.9 per cent by Bonney), with radiation alone (20 per cent), with a peak of 27.4 per cent in Grey Ward and Healy's figures, it seems to me evident that the combined treatment gives the patient a better chance than operation alone or radiation alone.

A short description of the extended vaginal operation, and the combination with introduction of radium at the end of the operation can be found in Pack and Livingston's excellent monograph on cancer treatment (Paul B. Hoeber, 1940).

I had the privilege of demonstrating my method in a moving picture at the meeting of the American Gynecological Society at Asheville, North Carolina, in 1938.

LUDWIG ADLER, M.D.

45 EAST 82ND STREET

Reply by Dr. Anspach

To the Editor:

I am sorry that Dr. Adler's work was overlooked. It was quite certain that some one would be forgotten at the moment. I was impressed with his reports. Unfortunately, in preparing the review my attention was focused on the abdominal operation, and the vaginal one completely slipped my mind. I am glad that Dr. Adler has made this very valuable addition to my paper.

BROOKE M. ANSPACH, M.D.

1827 SPRUCE STREET
PHILADELPHIA, PA.

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Chicago, Illinois, by the entire Board from Monday, May 6, through Saturday, May 11, 1946. The Palmer House in Chicago will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing directly to the Palmer House.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1946.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty, under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1947 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL. TITUS, M.D.

The following diplomates have been certified and are added to the previously published list: Dr. Frederiek W. Bald, 1217 Union Industrial Building, Flint, Michigan; Dr. John P. Redgwick, 1530 Medical Arts Building, Omaha, Nebraska.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Edward A. Schumann, Philadelphia, Pa. *Secretary*, Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting Hershey, Penn., June 3-6, 1946.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Lewis F. Smead, Toledo, Ohio. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1946.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting Chicago, Ill., October, 1946.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Robert A. Ross, Durham, S. C. *Secretary*, T. J. Williams, University, Va. Annual meeting on steamer, Tampa to Havana, Feb. 7-8, 1947.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Philip F. Williams, Philadelphia, Pa. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas Tex. Annual meeting San Francisco, July 1-7, 1946.
- New York Obstetrical Society.** (1863) *President*, R. A. Hurd. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Bernard Mann. *Secretary*, John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, James E. Fitzgerald. *Secretary*, Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, John J. Madden. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Carroll J. Fairor. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Charles Hunt. *Secretary-Treasurer*, Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James S. Taylor. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, George Van S. Smith. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Roy J. Heffernan, Brookline, Mass. *Secretary*, Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Goodrich C. Schaffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

- New Orleans Obstetrical and Gynecological Society. (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society. (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society. (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists. (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Robert B. Kennedy. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists. (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists. *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society. *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society. (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society. (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology. (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society. (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology. (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society. (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Sehamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society. (1944) *President*, Sylvester Goodman. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held last Wednesday of each month.
- Nassau Obstetrical Society. (1944) *President*, George B. Granger. *Secretary*, William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bi-monthly from October to May.
- Bronx Gynecological and Obstetrical Society. (1924) *President*, Harry Gordon. *Secretary-Treasurer*, J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society. (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society. (1922) *President*, J. Milton Singleton. *Secretary*, Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.
- Los Angeles Obstetrical and Gynecological Society. (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society. (1932) *President*, Frank Locke, Winston-Salem. *Secretary*, Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada. (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, Ont. Meetings held annually, date of next meeting to be announced later.

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Original Communications

AN INQUIRY INTO THE CAUSES OF BREECH PRESENTATION

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IN 1940 C. Keith Vartan published a short but provocative paper on the etiology of breech presentation. He introduced his subject by reviewing the causes of breech presentation listed in current textbooks; namely, prematurity, placenta previa, hydrocephalus, multiparity, multiple pregnancy, contracted pelvis, and pelvic tumors. Then he said, "What struck me and still impresses me concerning the etiology of breech presentation is that most of these factors which are reputed to be causes seldom occur. I concluded, therefore, that either the 'cause' is so rare as to be almost a chance coincidence or that the cause in almost every case is unknown." He presented data derived from 969 breech cases to support this conclusion.

The present study of the etiology of breech presentations is a repetition and elaboration of Vartan's work.* At the Philadelphia Lying-In Hospital in the ten years following Jan. 1, 1933, there were 1,184 breeches among 25,170 deliveries. Excluding breech deliveries after internal podalic version and excluding all twins presenting by the breech, there remain 911 single "primary" breech presentations delivered normally or by cesarean section. In the analysis to follow, each of the factors usually alleged to cause breech presentation will be critically examined in the light of these 911 case histories.

1. *Multiple pregnancy* is not dealt with in the study proper since the inclusion of twins, triplets, and quadruplets would confuse rather than clarify an understanding of the mechanism of breech lies. However, it may be said in passing that common sense leads one to expect twins to lie in utero in a head-to-breech position, each facing medially with relation to the mother. It is as natural a fit as a pair of shoes in a shoe box lying heel-to-toe, soles out, soft sides in. Multiple pregnancy undoubtedly disposes to the breech presentation of one baby.

*Since the present study was submitted to the editor, Dr. Vartan has published a continuation of his own work (*J. Obst. & Gynaec. Brit. Emp.* 52: 417, 1945). In this second article Vartan uses a different approach from the author, but arrives at similar conclusions.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

2. *Prematurity* is an important factor in breech presentation. To be more specific, small babies, regardless of the period of gestation, are more likely to present or to be delivered as breeches. It is a fact which anyone may easily verify, and which Weisman has proved by x-ray studies, that breeches are common until the last month or so of pregnancy and that spontaneous conversion to a cephalic presentation is the rule as term approaches. Hence, if one is to determine the mechanism producing breeches at term, it is essential to separate the premature or small babies arbitrarily from the mature. Reference to Table I will show that the incidence of breeches is greatest among infants weighing less than 2,500 grams (5½ pounds) at birth, and since this weight is commonly accepted as the dividing line between prematurity and maturity, most of this study will be concerned with single pregnancies terminating in a breech baby weighing 2,500 or more grams.

It is apparent that the proportion of breeches in any hospital series will increase if smaller babies are included (Table II). This probably explains the varying incidence of breeches in different clinics.

TABLE I. SHOWING THE INCIDENCE OF BREECH PRESENTATION IN RELATION TO FETAL WEIGHT IN 4,138 DELIVERIES OF SINGLE BABIES

GRAMS	UNDER 1,000	1,000- 1,499	1,500- 1,999	2,000- 2,499	2,500- 2,999	3,000- 3,499	3,500- 3,999	OVER 4,000	TOTALS
Breech presentations	15	12	8	13	26	60	19	8	161
All presentations	59	34	46	165	736	1,659	1,104	335	4,138
Per cent breech	25	35	17	8	3.5	3.6	1.7	2.4	3.9

TABLE II. SHOWING HOW THE INCIDENCE OF BREECH PRESENTATIONS INCREASES IF SMALLER FETUSES ARE INCLUDED IN THE SERIES (DERIVED FROM TABLE I)

GRAMS	ALL WEIGHTS	1,000 OR MORE	1,500 OR MORE	2,000 OR MORE	2,500 OR MORE	3,000 OR MORE	3,500 OR MORE	4,000 OR MORE
Breech presentations	161	146	134	126	113	87	27	8
All presentations	4,138	4,079	4,045	3,999	3,834	3,098	1,439	335
Per cent breech	3.9	3.6	3.3	3.1	2.9	2.8	1.9	2.4

Whether breeches tend to produce premature labor, or vice versa, will not be questioned here. The fact is that small babies, as well as twins, are often breech at birth. The more interesting question is, why do some mature infants present as breeches?

3. *Multiparity* is a stated cause of breeches. The relation is difficult to determine, for as parity increases, age increases, the average size of babies increases, and other confusing factors enter the problem. As a preliminary study of the effect of multiparity, the incidence of breeches was determined in 1,000 consecutive primiparas, 1,000 consecutive secundiparas, and so on. The original project of securing data for 1,000 patients in each rank of parity could not be completed, but the figures from 5,262 histories are displayed in Table III. After studying them and considering all the possible concomitant factors, the reader will probably not be particularly impressed with the importance of multiparity as a cause of breech presentations.

It is said in support of the contention that multiparity predisposes to breeches that more than 50 per cent of breeches occur in multiparas. This is easy to believe since 51 per cent of all patients in our clinic are multiparas (Table IV). Yet oddly enough, 55 per cent of all breeches over 2,500 grams were born to primiparas. Calculations of this sort are frequently made and sometimes quoted but upon reflection have little to do with solving the relation between multiparity and breeches.

Nandi strikes nearer the root of the problem when he points out that if the incidence of breeches is 3 per cent in the first pregnancy and 3 per cent in each subsequent preg-

TABLE III. SHOWING THE INCIDENCE OF BREECH PRESENTATION IN RELATION TO PARITY IN 5,262 DELIVERIES OF SINGLE BABIES

PARITY	ALL BABIES			BABIES OVER 2,500 GRAMS		
	NUMBER OF DELIVERIES	BREECHES NUMBER	PER CENT	NUMBER OF DELIVERIES	BREECHES NUMBER	PER CENT
1	1,000	44	4.4	913	31	3.4
2	1,000	31	3.1	914	19	2.1
3	1,000	38	3.8	893	32	3.6
4	1,000	35	3.5	546*	12	2.2
5	500	24	4.8	243	6	2.5
6	300	16	5.3	140	5	3.6
7	156	5	3.2	67	0	0.0
8	125	7	5.9	55	2	3.6
9	81	4	4.9	24	2	8.0
10	51	2	3.9	20	2	10.0
11						
or more	49	8	16.0	17	2	12.0
Total	5,262	214	4.07	3,832	113	2.95

These figures were derived from a chronological list of deliveries in the following way: Data for fetal presentation and weight were recorded on every case, regardless of parity, until 1,000 para i patients had been tabulated; thereafter data were recorded for all patients except para i, until a total of 1,000 para ii patients had been tabulated; thereafter para i and ii were omitted and the tabulation was continued until data accumulated for 1,000 para iii, and so on. The original plan was to secure data for 1,000 patients in each rank of parity. This project was abandoned after 5,262 patients were listed, because of the realization that a clinic which records its data on punch-cards could, with the use of business machines, tabulate an enormous mass of data of this sort in a few hours. To complete even a small series of 10,000 cases by hand-sorting would have required additional weeks.

(*Reference to the table shows that about 90 per cent of babies born to paras i, ii, and iii weighed over 2,500 grams. A smaller percentage of babies born to patients of higher parity are listed as weighing over 2,500 grams because tabulation of fetal weights was discontinued.)

TABLE IV. COMPARING THE PARITY OF MOTHERS HAVING BREECH PRESENTATIONS WITH THE PARITY OF THE GENERAL POPULATION OF THE HOSPITAL

MOTHER'S PARITY	1	2	3	4	5	6	7 OR MORE	PER CENT	NUMBER OF PATIENTS
All presentations	49%	34%	10%	3%	2%	1%	1%	100	2,051*
All breeches	54%	21%	12%	4%	3%	2%	4%	100	910†
Breeches over 2,500 grams	55%	21%	11%	4%	2%	3%	4%	100	677

*A chronological series of deliveries.

†911 breeches in present study (parity not stated for one patient).

TABLE V. SHOWING THE INCIDENCE OF BREECHES IN THE SECOND PREGNANCY OF 127 PATIENTS WHOSE FIRST BABY WAS BREECH (GROUP A). TWO CONTROL SERIES ARE PRESENTED (GROUPS B AND C). GROUPS A AND B ARE LIMITED TO PATIENTS WHO HAD TWO BABIES EACH WEIGHING OVER 2,500 GRAMS. GROUP C IS LIMITED TO PATIENTS WHOSE SECOND BABY WEIGHED OVER 2,500 GRAMS

GROUP	SOURCE OF DATA	BREECH PRESENTATIONS	
		PARA I	PARA II
A	127 patients para ii whose first baby was a breech (taken from the general population of the hospital)	127 (100%)	12 (9.4%)
B	127 patients para ii whose first baby was a cephalic (taken from histories of author's private patients)	None (0%)	3 (2.4%)
C	914 patients, para ii (data from Table III, a sample of the general population of the hospital)	No data	19 (2.1%)

If this table is a reliable guide, it appears that a mother whose first baby is breech has a greater than average chance of having a breech with her second pregnancy provided that both babies weigh over 2,500 grams.

TABLE VI. PRESENTING DATA RELATING TO THE PROBABILITY OF MORE THAN ONE BREECH BIRTH OCCURRING DURING THE LIFETIME OF A MULTIPAROUS PATIENT

1,300	409 mothers bore at least one breech baby over 2,500 grams and at least one other baby over 2,500 grams. Excluding twins these women bore a total of 1,300 infants
- 409	Subtracting one breech baby for each mother, we are left with 891
891	births in addition to one breech birth
- 598	598 babies are excluded because they weighed less than 2,500 grams or because data are not available (born elsewhere)
293 (100%)	Babies over 2,500 grams remain
267 (91.1%)	Cephalic presentations
26 (8.9%)	Breech presentations

If the chance of a breech birth (for infants over 2,500 grams) be taken as 3 per cent, this tabulation makes it appear that a mother who has once borne a breech baby has a greater than average chance of another breech presentation if additional children are born.

nancy, it follows that women who have the largest number of children will ultimately have the greatest number of breeches. To put it another way: the more often one flips a coin the greater the chance of eventually getting "tails."

Although the effect of multiparity in predisposing to breeches cannot be solved from the data on the series presented here, some related problems can be studied. For instance, do breeches tend to be repeated in the same individual? Table V shows that breeches recurred in secundiparas more often than anticipated. But the series is too small to justify conclusions. Table VI attempts to answer the question whether breeches tend to recur in the same mother regardless of her parity at the time of any breech birth and regardless of the total number of children she bears. This involved question requires for solution a mass of information difficult to assemble. Our own data are incomplete but they seem to show that mothers who bear one breech baby have, among their other babies, an incidence of breech births which is higher than the breech incidence for the hospital as a whole. Thus it appears that some patients have an individual tendency to bear breech babies.

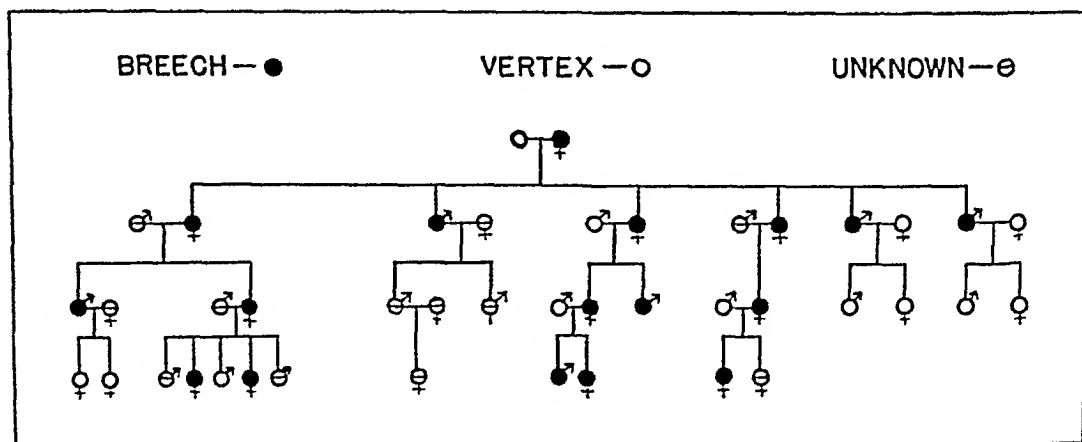


Fig. 1.—(Redrawn from Cartledge and Hancock.) The second generation consists of three sons and three daughters, all breech births. Note that every subsequent breech birth occurred in the offspring of the daughters.

4. *Hereditary tendency to breech* might seem in the domain of folklore were it not for the report of Cartledge and Hancock whose diagram is reproduced in Fig. 1. The recurrence of breeches in this family is greater than chance (calculated at 3 per cent) would account for.

5. *Contracted pelvis* is an old explanation for breech presentations and not a very sound one. To begin with, pelvic contraction is extremely difficult to define, especially in the case of breeches. In collecting data from our own records the writer accepted the state-

ment that the patient had a contracted pelvis. No attempt was made to verify, correct, or justify the criteria in vogue when the record was made. Hence "contracted pelvis" is used in this paragraph in the loosest possible sense and includes pelves described as flat, android, asymmetrie, platypelloid, justo minor, rachitic, and funnel. Among mothers bearing 677 mature breech babies there were 75 "contracted pelves," or 11 per cent. Phrased otherwise, this means that of all the breech deliveries observed 89 per cent could not be attributed to contracted pelvis. Therefore pelvic shape is not a striking factor in the etiology of breeches. If it were, one would find that multiparous patients with pelvic contractions had a high incidence of repeated breech presentations. Apparently they do not. (Table VII.)

TABLE VII. SHOWING THE INCIDENCE OF "CONTRACTED PELVIS" AMONG MOTHERS BEARING BREECH INFANTS AND THE INCIDENCE OF REPEATED BREECH BIRTHS IN MOTHERS WITH "CONTRACTED PELVIS" (ALL DATA LIMITED TO BABIES OVER 2,500 GRAMS)

Total number of breech babies	677	100%
Number of breech births associated with "contracted pelvis"	75	11%
Number of mothers with "contracted pelvis" bearing babies of known polarity in addition to one breech baby	22	
Total number of babies born to these 22 mothers	52	
Subtracting 1 breech baby for each mother	22	
There remain 30 additional babies	30	100%
Of these 3 were breeches (2 normal babies and 1 dead for one month before delivery)	3	10%

Tables V and VI show that breech births are repeated in about 9 per cent of all multiparas. If "contracted pelvis," as defined in the text, plays a part in causing breech presentations, we should expect to find a remarkably high incidence of breeches among multiparas with contracted pelves. On the contrary, we find in the table above that multiparas with contracted pelves have only a 10 per cent incidence of repeated breech births. Accordingly, these tabulations do not support the idea that presentations are influenced by the structure of the maternal pelvis.

TABLE VIII. SHOWING THE INCIDENCE OF BREECH PRESENTATION AMONG 231 HYDROCEPHALIC INFANTS (WHETHER INTERNAL OR EXTERNAL HYDROCEPHALUS NOT SPECIFIED) AND AMONG 197 ANENCEPHALIC INFANTS (COURTESY OF DR. RAYMOND L. YOUNG)

	GRAMS	UNDER 500	500-999	1,000-1,499	1,500-1,999	2,000-2,499	2,500-2,999	3,000-3,499	3,500-3,999	4,000-4,499	OVER 4,500	ALL WEIGHTS	2,500 AND OVER
Hydro-cephalics	Cephalic	1	4	5	12	30	36	43	27	10	1	169	117
	Breech	0	3	2	5	10	11	17	6	3	5	62	42
	Total	1	7	7	17	40	47	60	33	13	6	231	159
	Per cent Breech											27	26
Anen-cephalics	Cephalic	1	25	41	36	15	22	15	5	2	0	162	44
	Breech	2	5	9	5	4	3	6	1	0	0	35	10
	Total	3	30	50	41	19	25	21	6	2	0	197	54
	Per cent Breech											18	19

6. *Gross fetal abnormalities* are often associated with breeches. Through the kindness of Dr. Raymond L. Young I am permitted to display data which he collected in collaboration with Dr. Edith Potter of the Chicago Lying-in Hospital. The data were derived from autopsies on 1,705 malformed fetuses and infants. We see in Table VIII that 26 per cent of hydrocephalics and 18 per cent of anencephalics weighing over 2,500 grams delivered as breeches. So these fetal abnormalities predispose in some way, and perhaps not in the obvious way, to breech presentation. However, neither hydrocephalus, anencephalus, nor other gross abnormalities play a very great part in producing breech lies in a large series of breeches. Among 677 breech babies over 2,500 grams in our series, there were only 7 hydrocephalics and 2 anencephalics. There were also two infants with large abdominal tumors due to polycystic kidneys.

7. *Placenta previa* is another stated factor in breech births. Only 8 cases of placenta previa were recorded in 677 breech births.

8. *Pelvic tumors* are reputed to cause breech presentation. Possibly all the pelvic tumors which occurred were not revealed by the present survey. Be that as it may, only 4 were mentioned in the 677 histories. Even if it is admitted that these tumors caused the breech lie, they account for only 0.6 per cent of all the breeches observed. And if the actual number of pelvic tumors was several times as great as the recorded number, these tumors still could account for an insignificant percentage of breech births.

9. *A uterine anomaly*, particularly bicornate uterus, is often associated with faulty presentation. In 35 cases of pregnancy in anomalous uteri, Smith found 15 breeches and 6 transverse lies. Rosenbloom's patient with a bicornate uterus had 2 breech and 2 transverse presentations in 7 term pregnancies. But incomplete fusion of the Müllerian ducts is rare; Smith estimates the incidence at one in 1,500 obstetric patients. Four cases were observed in the present series of 677 breeches, and in addition there was one case of septate vagina which may have been accompanied by a divided uterus.

10. *Uterine scars*: The influence of a uterine scar on breech presentations was considered. An examination was made of 100 records chosen at random of patients who had two cesarean sections. Only one patient had a breech lie when the second cesarean was performed.

11. *Maternal obesity* is alleged to increase the incidence of breeches. No statistics are available for our patients. However, Odell and Mengert report 5.5 per cent breeches (over 1,500 grams) among 687 deliveries of patients weighing 200 or more pounds. This percentage probably includes twins, and babies delivered after internal podalic version. If so, the incidence of breeches among obese patients is not remarkably high.

12. *Maternal age* is said to be a factor in breeches. If the question is to be fairly examined, any effect of multiparity upon the incidence of breeches must be eliminated. Therefore, data from elderly primiparas only will be considered. The incidence of breeches in primiparas of 35 years and over in this clinic is 9 per cent (Roeder, 113 patients). The data are not divided according to fetal weight so it may be presumed that the percentage includes infants of all weights. It seems not improbable that older primiparas have a somewhat greater tendency to breech presentations.

13. *Polyhydramnios* is reputed to be responsible for breeches, probably on the theory that the distended uterus offers more opportunity for spontaneous version or that there is less effective application of forces tending to press the fetus into the pelvis. Hydramnios is an elusive subject; as in the case of contracted pelvis, the first problem is definition. Polyhydramnios means excessive fluid, but how much is excessive? An amount which would be quite normal for a woman carrying a large baby might be decidedly excessive if the baby were small. So the relation of polyhydramnios to breech presentation depends not so much upon the measurable volume of fluid but upon the relation between the volume of the fluid and the volume of the baby. Measurements of this sort are not available in the present series of cases. Furthermore, polyhydramnios is so often associated with fetal malformation that it would be difficult to determine which factor, excessive fluid or malformation, was primarily responsible for the presentation.

At this point we may pause to evaluate the total effect of the factors which have thus far been considered as possible causes of breech presentations:

Multiple pregnancy	-----	admittedly a factor
Prematurity	-----	admittedly a factor
Multiparity	-----	a doubtful factor
Hereditary tendency	-----	possibly a factor
Uterine scars	-----	probably not a factor
Obesity	-----	probably not a factor
Elderly primiparas	-----	possibly a factor
Polyhydramnios	-----	possibly a factor

The more commonly accepted etiological influences are listed in Table IX. It is unlikely that many pelves are sufficiently contracted to effect the presen-

tation of very small babies, yet the incidence of "contracted pelvis" is about the same among mothers of babies weighing 210 to 2,499 grams as it is among mothers of mature babies. This observation further weakens the argument that pelvic architecture plays an important part in determining the presentation. Be that as it may, by invoking all the causes for breech presentation which seem to have a calculable importance, we have accounted for only 15 per cent of breech births of mature single babies. (Table IX.) Therefore, it

TABLE IX. SHOWING THAT THE CLASSICAL EXPLANATIONS FOR BREECH PRESENTATION ACCOUNT FOR ONLY 15 PER CENT OF BREECHES OBSERVED

	BABIES OVER 2,500 GRAMS		BABIES UNDER 2,500 GRAMS	
	(NO.)	(%)	(NO.)	(%)
"Contracted pelvis"	75	11.1	24	10.2
Gross fetal anomalies	11	1.6	10	4.3
Placenta previa	8	1.2	9	3.9
Pelvic tumors	4	0.6	1	0.4
Uterine anomalies	4	0.6	2	0.8
No demonstrable factor	575	84.9	188	80.3
Totals	677	100.0	234	100.0

is clear that factors other than those classically recognized must be at work. An attempt will now be made to discover these unrecognized factors.

14. *Fetal activity* is seldom mentioned in the etiology of presentation. However, if a clinician purposefully inquires about the degree of fetal activity at each antepartum visit, he will note that when relative inactivity is reported the baby is often found in a breech presentation. Whether fetal activity decreases before or after the baby assumes the breech presentation has not been determined. Also, we often find that babies which are languid after birth, for example some hydrocephalies, were delivered as breeches. Many of these are described as "inactive" babies before birth. In this connection two of my own cases come to mind. Both were breech babies with large lumbar meningoceles, both had motor paralysis of the lower extremities and died some days after delivery. One cannot avoid the thought that inability to move the legs contributed to their breech presentations. Going further, we realize that babies which die in utero weeks before birth not uncommonly are delivered as breeches. It is reasonable to believe that maimed babies who have impaired powers of motion, and babies whose movement is limited by extension of the legs would have less chance of extricating themselves from a breech lie by their own efforts than vigorous babies with flexed legs.

15. *Extended legs* (frank breeches) have long been recognized as the commonest type of the breech presentation. It has also been realized that external cephalic version of breech babies is difficult when the legs are extended, probably because of the "splinting" effect of the legs. After considering these facts, Vartan developed the idea that extension of the legs might be the primary cause of breech presentations. His data are compared with our own in Table X. By this method of tabulation some 60 per cent of breeches are explained, whereas the "classical factors" account for only 15 per cent of all the cases observed (Table IX). The suggestion that extended legs cause breech presentations is appealing but requires examination.

To begin with, a comparison was made between the incidence of extended legs in breech and cephalic presentations at term. At least 62 per cent of breech babies in this series had extended legs when they were delivered (Table XII). The percentage is probably higher, for some babies were delivered as "half-frank" presentations; in our records these were usually designated simply as footlings. To determine the incidence of extended legs in cephalic presentations the writer reviewed a random group of x-ray films taken at or near term (Table XI). There is no reason to believe that any unsuspected "selection" in this group of films affects the percentage of extended and flexed legs observed.

TABLE X. COMPARING TWO SERIES IN WHICH THE ETIOLOGICAL FACTORS ARE SET FORTH IN ACCORDANCE WITH VARTAN'S EMPHASIS ON THE IMPORTANCE OF EXTENDED LEGS

ORDER	VARTAN'S SERIES OF 969 BREECHES MINUS CASES OF MULTIPLE PREGNANCY AND PRE-MATURE INFANTS			PRESENT SERIES OF 911 SINGLE BREECHES MINUS INFANTS UNDER 2,500 GRAMS AND THOSE IN WHICH THE TYPE OF BREECH PRESENTATION WAS NOT STATED	
		(NO.)	(%)	(NO.)	(%)
1	Extended legs	362	56	249	63
2	Gross fetal anomalies	21	3	3	1
3	Fibroids	2	-	1	-
4	Placenta previa	31	5	1	-
5	Disproportion	13	2	15	4
6	No abnormality recorded	222	34	128	32
	Total Cases	651	100	397	100

In tabulating the author's series it was necessary to assign an arbitrary "order of etiological importance" since more than one factor was present in some cases. Accordingly the factors are ranked as shown, with extended legs assigned the greatest importance and contracted pelvis the least importance.

TABLE XI. SHOWING THE INCIDENCE OF EXTENDED LEGS IN X-RAY FILMS OF PREGNANCY AT OR NEAR TERM

Number of films examined	123
Legs not visible (blurred by fetal movement, not included on the film, etc)	-27
	96
Breech presentations (all had extended legs)	-4
Cephalic presentations	92
Both legs flexed at the knee	89
One or both legs extended at the knee	3
	100%
	97%
	3%

None of these films was taken for the purpose of investigating fetal attitude. They were made as an aid in the diagnosis of placenta previa, contracted pelvis, disproportion, and for other clinical reasons. All the infants ultimately were delivered in the same presentation as that shown on the films. The three babies whose presentation was cephalic but who had extended legs were delivered within forty-eight hours after the films were made; none rotated to a breech lie.

TABLE XII. SHOWING THE TYPE OF BREECH PRESENTATION AT THE TIME OF DELIVERY IN 377 INFANTS OVER 2,500 GRAMS AS RELATED TO THE DURATION OF GESTATION

TYPE OF BREECH (%)	WEEKS' GESTATION (ACTUALLY, WEEKS SINCE MENSTRUATION)							TOTALS	
	36	37	38	39	40	41	42	CASES	PER CENT
Frank	28	50	55	63	65	66	68	233	62
Single foot-ling	36	7	20	14	17	14	14	63	17
Double foot-ling	36	29	22	19	14	14	9	61	16
Complete	0	14	3	4	4	6	9	20	5
Total %	100	100	100	100	100	100	100	377	100
Frank plus single foot-ling	64	57	75	77	82	80	82	296	79

Since some of the single footlings are known to have had one leg extended ("half-frank" presentation) and others may have had one leg extended, data are shown for frank-breech-plus-single-footlings as well as for frank breech. The percentage of frank breeches is usually given as 80 per cent or more. The writer cannot explain the low incidence of frank breeches in the present series unless it arises in this way: There were 677 babies (over 2,500 grams) in the series, but the type of breech and the duration of gestation were stated only in the 377 cases shown above, leaving 300 breech deliveries of unknown type. Experience with hospital records teaches medical statisticians that, in general, unusual findings are more apt to be recorded than normal findings. Since the usual breech presentation is frank, while footling and complete breeches are exceptional, it may be that most of the 300 breech deliveries of unstated type were frank. If so, the oddly low incidence of frank breeches in the table above is understandable.

It has been shown in Table I that as gestation advances or the weight of the fetus increases, the incidence of breeches decreases. Among breeches the incidence of footlings also decreases as gestation advances (Table XII). Recalling that external cephalic version is most difficult for the obstetrician to accomplish when the legs are extended, hence least difficult when they are flexed, it seems reasonable to suppose that spontaneous version also occurs more easily when the legs are flexed. If this is so we may explain the decreased incidence of footlings in late pregnancy by assuming that most of them have undergone spontaneous version and are delivered as cephalic presentations.

16. *Cord complications*, such as short cords, or coils of cord around the extremities, may account for some breeches by interfering with spontaneous version. Prolapse of the cord occurred in 15 of the 677 breech deliveries. Twelve prolapses occurred in footlings, three in complete breeches, and not one in frank breeches. The absence of prolapse among the frank breeches (which constituted two-thirds of all breeches delivered) may be due to the fact that the frank breech more nearly fills the cervix than other types of breech presentation. However, if it could be shown that the slack length of the cord was decreased by its being coiled about the body or extremities, we should have a possible explanation both for the breech lie (by interfering with free motion of the extremities or with free longitudinal rotation of the fetus) and for the absence of prolapse. (Mengert and Longwell have shown that prolapsed cords are usually long cords. If a long cord should be coiled about the baby so that little slack remained it would seem unlikely that prolapse could occur.)

17. *Hypothetical explanation of breech presentations*: By piecing together the fragmentary data available, we can now form a rough idea of the gyrations of the fetus which lead to breech deliveries. Perhaps the order of events is something like this:

In the first trimester of pregnancy, the fetus is suspended in a spherical body of fluid of greater volume than itself and it manifests no consistent polarity. As the fetus grows, its body becomes larger in relation to its head, and its total volume increases in relation to the volume of the surrounding fluid. Moreover, as pregnancy progresses, the shape of the uterine cavity changes from spheroid to ovoid. At the same time the center of gravity and the center of buoyancy of the fetus are altered so that it tends to lie head downward rather than breech downward. If labor occurs at the thirty-second week of gestation, counting forty weeks as full term, or to use a more objective index of fetal age, when the fetus attains 1,500 grams, the factors influencing polarity produce a breech presentation in about one-sixth of the cases delivered (Table I).

The typical posture or "fetal attitude" is depicted at this age as extreme flexion of the neck, the body, the thighs, the legs, and the arms. From this starting position any motions must be toward a position of extension. Possibly full extension of the legs occurs often during this period and as long as there is ample room for free movement the legs easily return to the flexed attitude. If it happens that the amniotic fluid suddenly escapes, the uterus will contract and the fetus will be caught and delivered in his presentation of the moment. As we have seen, this is frequently a breech presentation for babies under 2,000 grams (Table I). However, if premature labor does not occur, the fetus increases in size and vigor while the space available for movement of the extremities decreases. The legs less readily become extended but once extended return to the flexed position with difficulty. As long as the legs are flexed it may be presumed that the fetus can "scramble" around. He is much like a squirrel in a rotating cage, but in this case the cage is fixed while the fetus is free to rotate inside it. For reasons by no means clear the fetus tends to assume a cephalic presentation in late pregnancy.* At term, about 97 per cent of babies are cephalic, about 3 per cent breech. Since the incidence of flexed legs at term is high among cephalic

*That gravity is effective in predisposing to cephalic presentations seems to be accepted. However, one should remember that in such horizontal animals as the cow and the mare, vertex deliveries are the rule and it would seem that in these animals the effect of gravity upon presentation would be minimal. I should not be astonished to be informed that long before man assumed the upright posture cephalic presentations were the rule. Perhaps the fetus faces the exit for the same reason that a person in an elevator faces the exit, or vice versa.

babies (Table XI) and low among breeches (Table XII), it is reasonable to assume a causal relation between extension of the legs and breech presentation. If we determine the incidence of extended legs among breech babies in relation to the duration of gestation, we find more and more frank breeches as term is approached (Table XII). This may mean that most of the breech infants with flexed legs have already been delivered, or it may mean that they have managed to convert themselves to cephalic presentations, leaving mainly the babies with extended legs helplessly caught in the breech lie. Either interpretation explains the decreasing incidence of breeches as compared with cephalics and of footling breeches as compared with frank breeches as gestation advances. Premature rupture of the membranes is particularly common if the foot lies over the internal os in such a way that motion of the legs may thrust a toe through the membranes. If this happens, the fetus is gripped by the contracting uterus and is born as a footling. Given a little more time these babies might have succeeded in converting themselves to a cephalic presentation.

Thus far we have assumed that there has been no interference with fetal movements and that the contour of the uterine cavity has been ovoid. However, it must sometimes happen that the cord is coiled about the body or neck, looped over the shoulder, or wrapped about an extremity. In such cases, spontaneous podalic version may be impossible either because the fetus is tied in a given position or because an entangling cord limits movement of the legs. It is in this way that coils of cord or short cords may be responsible for some breech presentations. In rarer instances the uterus itself may be faulty, for instance a septate uterus or a bicornate uterus. In such uteri one would not expect to find a perfectly ovoid cavity and there should be less likelihood of spontaneous version (Smith reports 47 per cent breeches in anomalous uteri). The contour of the uterine cavity may also be altered from without by the pressure of ovarian cysts or other pelvic tumors, or it may be altered from within by a submucous myoma or an abnormally implanted placenta.

In still other cases the uterus and cord offer no hindrance to version but the fetus itself is at fault. As a result of hydrocephalus, meningocele, dysplasia of the hips, cerebral agenesis, or some other congenital defect, its intrauterine vigor may be impaired. These defective babies, many of them breeches, are often accompanied by polyhydramnios, which is usually accepted as an explanation for their abnormal presentations. For my part, at present I am prepared to believe that the breech lie in such cases is due as much to uncoordinated or ineffective fetal activity as to excessive fluid.

The matter of recurrent breech births remains. In the majority of cases, it is as easy to believe that babies born of the same mother have similar peculiarities of skeletal structure or of intrauterine activity which account for their type of presentation, as it is to believe that the repeated breech births are due solely to a physiologic or anatomic characteristic of the mother.

Summary

Two aspects of the etiology of breech presentation have been considered. First, it has been found that the "classical factors" (contracted pelvis, pelvic tumors, placenta previa, and fetal malformation) in the aggregate account for only one-sixth of the breech births among mature single infants. Second, the data which have been assembled suggest that extension of the legs may be a causative factor rather than a resultant effect in breech presentations. The mechanism by which extension of the legs may operate to affect the presentation has not been fully discussed here. It is the writer's hope that within a few years he will be prepared to report current experiments which deal with the effects of gravity and of the contour of the fetal mass upon polarity. At that time, a review and correlation will be made of many important fundamental publications which have not been alluded to in the present study.

Statistics

Incidence of Breech Presentation.—

Cannell and Dodek	3.4%	in 16,166 deliveries
Danforth and Galloway	3.3%	in 8,531 deliveries
Moore and Steptoe	2.8%	in 51,571 deliveries
Morton	3.53%	in 8,509 deliveries
Patton and Mussey	4.87%	in 6,195 deliveries
Walsh and Kuder	4.72%	in 29,683 deliveries
Waters	4.3%	in 20,000 deliveries
Rathbun	2.4%	in 250 patients 15 or more days past term

Incidence of Contracted Pelvis in Breech Presentations.—

Cannell and Dodek	1.0%	in 550 breeches
Gordon, Garlick, and Oginz	5.3%	in 3,241 breeches
Higgins	1.0%	in 550 breeches
Morton	5.2%	in 285 breeches delivered vaginally
Seeley and Siddall	2.9%	in 456 breeches over 2,500 grams
Siegel and McNally	34.7%	in 167 breeches
Walsh and Kuder	12.7%	in 55 breeches in primiparas over 35 years
	11.02%	in Clinie as a whole
Vartan	1.3%	in 969 breeches
	1.1%	breeches in 986 cases of disproportion

Incidence of Congenital Defects in Breech Babies.—

Cannell and Dodek	2.7%	in 550 breeches
Gordon, Garlick, and Oginz	1.6%	in 3,301 breeches
Siegel and McNally	1.2%	in 167 breeches
Vartan	2.1%	in 969 breeches

Incidence of Placenta Previa in Breech Presentations.—

Cannell and Dodek	1.3%	in 550 breeches
Goethals	1.8%	in 1,219 breeches
Waters	0.9%	in 675 breeches (full term)
Vartan	3.2%	in 969 breeches
	8.0%	breeches in 387 cases of placenta previa

Incidence of Breeches in Elderly Primiparas.—

Erving and Power	8.0%	in 199 patients
Nathanson	6.0%	in 186 patients
Roeder	9.0%	in 113 patients
Walsh and Kuder	6.73%	in 813 patients
Wahrsinger and Kushner	3.0%	in 111 patients

Incidence of Prolapsed Cord in Breeches.—

Cannell and Dodek	1.0%	in 550 breeches
Goethals	3.4%	in 2,093 breeches
Seeley and Siddall	3.3%	in 538 breeches
Siegel and McNally	3.0%	in 167 breeches

Elective External Version.—

Siegel and McNally advise against version on frank breeches
 Ryder says that failure in accomplishing external version is due first to delay in attempting it, and second to extended legs.

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AN EVALUATION OF THE TREATMENT OF THE PERSISTENTLY UNENGAGED VERTEX IN THE MULTIPARA

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THE successful spontaneous termination of labor in the average multipara occurs with such great frequency that the obstetrician approaches the intrapartum multiparous patient with assurance tinged perhaps with a little indifference. The apparent lack of severe soft part injuries, the shorter labor, even the spontaneous delivery of some faulty positions and presentations is admitted and may account for a false sense of security. At times, therefore, complications arise which are not anticipated and are frequently overlooked with a resulting mortality to mother, baby, or both.

In the present discussion an effort has been made to evaluate the causes for lack of engagement and the use particularly of version and breech extraction for this condition in the multiparous patient. Several cases have been included in which versions and breech extractions were performed because of the presence of an additional complication, namely, prolapse of the cord.

Lack of Engagement in Multiparas

Engagement is primarily the result of relaxation and retraction of the lower uterine segment with the consequent passive descent of the presenting part through the pelvic inlet. In the majority of primigravidas the presenting part begins to come into the pelvis about two or three weeks before term, while the average multipara starts labor with an unengaged head. When engagement has failed to take place in the primigravid patient, the obstetrician is sufficiently aroused and, therefore, rechecks all of the factors involved to determine any obvious reason for such lack of engagement. Vaginal examinations and, at times, suitable roentgenograms are employed to study the existing relationship of the fetal head to the pelvis. On the other hand, most multiparous patients when seen at the onset of labor are found to have the presenting part either floating or just dipping into the inlet. An overwhelming proportion of these will descend into the pelvis as labor advances; in others the station of the head may remain unchanged until labor is far advanced, and then, with a few strong contractions along with the rupture of the membranes, the head descends into the pelvis. There remains the occasional multipara, however, in whom engagement fails to occur even though labor is far advanced.

The conditions which militate against engagement are either of a functional or pathologic nature and merit some discussion. The relaxed abdominal wall of the multipara may permit a faulty direction of the fetal axis and uterine forces, the net results of which may be a lack of progress in the descent

of the fetal head. Furthermore, faulty positions and presentations are also favored, and so one may encounter marked asynelytism with a persistent parietal presentation, brow or face presentation, as well as the poorly flexed vertex in the occiput transverse or posterior position. Under these circumstances, functional in origin, delay in engagement may occur but subsequently may be overcome, either as a result of the driving powers of good uterine contractions or the correction of the fetal axis spontaneously or by a proper abdominal support. Flexion and molding will then permit the passage of the smaller diameters through the pelvic inlet. A large distended bag of forewaters may prevent engagement until it ruptures spontaneously or is ruptured artificially, after which descent may take place. However, with the rupture of the amniotic sac in the presence of an unengaged vertex, irrespective as to the cause, an additional hazard may be encountered, namely, a prolapsed cord. This complication may necessitate a rapid method of delivery in the interests of the baby unless restoration of the cord is possible, which in most instances cannot be readily accomplished, or unless the vertex can be brought through the pelvis very quickly. Again, the presence of an absolutely short cord or a relatively short cord may cause delay in engagement of the vertex. Many multiparas approach the onset of labor poorly prepared to go through the ordeal, as a result of overwork, insufficient rest, anemia, too many and too frequent pregnancies, as well as some constitutional inadequacies. These patients may have a long labor, the result of inertia uteri, and so delay in engagement may be noted in them as well.

Other factors preventing engagement are oftentimes associated with definite pathology, as for example, cephalopelvic disproportion, unretracted fibroids obstructing the pelvic inlet, extrauterine neoplasms notably dermoids, placenta previa, or monstrosities such as hydrocephalus.

The general attitude toward the intrapartum multipara has been one of watchful expectancy if her previous history revealed spontaneous deliveries or deliveries attended with no great difficulty. Thus, this patient may be permitted to continue in labor with little or no progress for a variable period before the true state of affairs is recognized. When should an accurate appraisal be made in this patient comparable to that in the primigravida with the unengaged head? It is felt that if the presenting part is not advancing into the pelvis when dilatation is almost complete, or has failed to enter the pelvis soon after dilatation is complete in the absence of a large forebag, such a patient should not be permitted to continue for an indefinite time without a thorough investigation. Obviously, most of the afore-mentioned factors should have been recognized even before the onset of labor. The most difficult cases to evaluate, however, are those in which the presenting part has failed to engage due to a relative disproportion. The relative size of a baby may be difficult to appraise in the presence of an obese and pendulous abdominal wall. In addition, the weights of previous offspring spontaneously delivered or delivered with little difficulty may be grossly exaggerated. In many instances these incorrect weights are due to the fact that these deliveries had taken place at

home where accurate scales were not available or the patient may have failed to remember the correct weights of her offspring and in a boastful sense has exaggerated them.

Irrespective of the cause for lack of engagement, the continuation of labor with lack of progress may result not only in maternal exhaustion, hemorrhage, and infection, but another complication which has potentialities equally as dangerous or more so, namely, a tight contraction ring and a tonic uterus with possible subsequent rupture. The unengaged head, then, in a multipara who has been neglected in labor becomes a real hazard not only in the para viii or ix, *grande multiparae*, but in those of a lesser parity as well. For the ultimate delivery of these patients, high forceps have now been completely discarded. Since version and breech extraction would seem to be the next most suitable procedure, with cesarean section less suitable, this study of multiparas with persistently unengaged vertices delivered by version and breech extraction was undertaken at Bellevue Hospital in order to evaluate the results.

Indications for Version and Breech Extraction

From January, 1933, to August, 1944, an eleven and one-half year period, there were 21 multiparas who were delivered by version and breech extraction because of a persistently unengaged vertex. There has been a definite diminution in the frequency of this operative procedure, the justification of which becomes more apparent with a study of the end results. The ages of the patients in this series varied from 24 to 48 years. There were 19 white patients and 2 Negro. The number of previous term pregnancies varied from one to nine with a mean of four. The babies' weights varied from 6 pounds, 3 ounces, to 10 pounds, 13 ounces, and 62 per cent were over 8 pounds. In 10 cases the weights of the babies were less than the weights of previous siblings. In 6 cases the present weights were greater, while in 5 cases no comparison could be made since the weights of the previous babies were unknown.

An evaluation of the 21 pelves revealed that 14 were considered clinically ample for small to average-sized babies, as determined by vaginal examination alone. In 3 of these cases large babies accounted for cephalopelvic disproportions, and due to lack of recognition of this condition, version and breech extraction resulted in stillbirths. Two of the 21 were considered ample clinically and this was substantiated by postpartum x-ray studies. Three were thought to be clinically ample but were subsequently found to be contracted by postpartum x-ray examination: one was an android pelvis with an anteroposterior diameter of 9.8 cm. and transverse diameter of 10.0 cm., and the other 2 were platypelloid, with an anteroposterior diameter of 9.2 cm. and transverse diameter of 14.6 cm. in one, and an anteroposterior diameter of 9.4 cm. and transverse diameter of 12.3 cm. in the other. In all of these 3 distorted pelves, stillbirths resulted. The final 2 pelves were not evaluated clinically but postpartum x-rays revealed them to be ample. As to the position of the vertices there were 6 in left occipitoanterior; 3 in left occipitotransverse; 1 in left occipitoposterior; 3 in right occipitoanterior; 4 in right occiput transverse; and 4 in right occipitoposterior.

The length of the first stage of labor varied from 2 hours to 45 hours, an average of 13½ hours. The length of the second stage varied from 15 minutes to 7½ hours, with an average of 2½ hours.

For study, the cases in this series were divided into four groups, depending upon the indication which existed for version and breech extraction in addition to the unengaged head. The first group (Table I) consisted of those patients in whom lack of progress was the indication. There were 9 such patients [S.F., R.E., M.M.(1), H.M., F.D.R., M.M.(2), S.K., L.C., M.S.(1)]. Secondary uterine inertia was noted in six of these patients [S.F., M.M.(1), H.M., F.D.R., L.C., M.S.(1)], in one of whom [M.M.(1)] a bag was employed after cessation of contractions for twelve hours. Preceding the version and breech extrae-

TABLE I. LACK

NO.	NAME	YEAR	AGE	RACE	PARITY	WT. OF PREV. BABIES (LB.)	POSITION	PELVIS	FIRST STAGE (HR.)	SECOND STAGE (HR.)
1	S. F.	1933	38	White	2	7 6	L.O.P.	Clinically ample	24	7½
2	R. E.	1933	41	White	4	9½ 8½ ? ?	R.O.A. poorly flexed	Clinically ample	9	3
3	M. M. (1)	1933	37	White	4	Unknown	L.O.A.	Clinically ample	45	3½
4	H. M.	1933	38	White	5	10 10 8 8 10	R.O.P.	Clinically ample	15½	6½
5	F. D. R.	1935	34	White	3	5 4 5	L.O.T.	Clinically ample	7	6

INTRAPARTUM COURSE	POST-PARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
After being in labor 11 hr. membranes ruptured spont. Secondary uterine inertia ensued which was not helped by 3 min. pituitrin. Same dosage repeated after 7 hr. with same result. Finally reached second stage. Small rim of cervix remained but was considered fully dilatable. After 7½ hr. without progress, version and breech extraction performed. Difficulty with aftercoming head was encountered. Piper forceps used. F.H. good until delivery	Morbid 101 scale	8½ lb.	S. B.	(1) Bilateral tentorial tears (2) Subtentorial hemorrhage (3) Rupture of liver (4) Hemorrhage into adrenals
Membranes ruptured spont. 4 hr. after onset of labor. Head floating. For 3 hr. cervix remained at 4 plus F. though fully dilatable. Head was above level of spines. Bailey-Williamson forceps applied but no progress made with traction. Version and breech extraction performed with difficulty with arms and aftercoming head. Piper forceps used. F.H. good until delivery	Non-morbid	8¼ lb.	Died within 15 min.	No P.M. obtained
Polyhydramnios. Membranes ruptured spont. 8½ hr. after onset of labor with release of much meconium-stained fluid. Secondary uterine inertia ensued with cessation of pains despite castor oil and quinine. After 12 hr. without pains, cervix was long, thick, external os 4 F., internal os 3 F., vertex floating. No. 4 Voorhees bag inserted. Poor labor pains followed. After 6½ hr. bag fell out. After 45 hr. of 1st stage, version performed under ether anesthesia. Breech did not progress and was followed after delay by breech extraction. Piper forceps for aftercoming head. F.H. lost 32 hr. after onset of labor	Non-morbid	9½ lb.	S. B.	(1) Bilateral laceration of tentorium cerebelli (2) Subtentorial hemorrhage (3) Cephalohematoma
After 14½ hr. cervix became 4 F. dilated and membranes were artificially ruptured. Following this, secondary uterine inertia ensued and cervix remained unchanged at 4 plus fingers and fully dilatable. Head remained high. Kielland forceps applied but removed because head was too high. Version and breech extraction performed. F.H. good	Morbid 100.4 scale	9¾ lb.	Living	
Pre-eclampsia. After first stage of 7 hr., cervix was fully dilated, head unengaged. After 1 hr. without progress, membranes were ruptured artificially. For 3 hr. patient was encouraged to bear down with pains with very little progress. It was felt that cause for delay was uterine inertia and not disproportion. After 4½ hr. of second stage, Kielland forceps were attempted without success. Version was then attempted at which time a contraction ring was discovered. Under deep anesthesia and adrenalin, relaxation occurred. Version and breech extraction performed with difficulty, due to extended arms. Condition of patient poor; third degree laceration encountered and patient went into shock. Cephalopelvic disproportion	Morbid 101° scale. Stormy clinical course. Suppurative thrombophlebitis with septic pulmonary infarcts. Died suddenly 31st day	9 lb.	S. B.	<i>Mother:</i> (1) Thrombosis of left pulm. art. (2) Thrombotic infarction of lung (3) Fistula of bladder (4) Abruption of bladder from pubic attachment (5) Multiple foci of suppurative nephritis (6) Well-involved normal P.P. uterus <i>Baby:</i> (1) Fracture dislocation of cervical vertebrae (2) Hemorrhage into spinal canal (3) Tentorial tear (4) Aspiration of amniotic fluid

TABLE I

NO.	NAME	AGE	YEAR	RACE	PARITY	WT. OF PREV. BABIES (LB.)	POSITION	PELVIS	FIRST STAGE (HR.)	SECOND STAGE (HR.)
6	M. M. (2)	1935	46	White	3	8 8 9½	L.O.A.	Clinically unknown. X-ray P.P.: gynecoid with an- thropoid tendency	20	2
7	S. K.	1936	24	White	1	Unknown	L.O.T.	Clinically ample. P.P. x-rays: gynecoid A.P. -11.3 T. -13	2	3½
8	L. C.	1939	34	White	6	8 7 6½ 6 7 7	R.O.T.	P.P. x-ray: gynecoid with platy- pelloid A.P. -10.3 T. -13	18	1¾
9	M. S. (1)	1940	35	White	6	Largest 8	R.O.P.	Clinically ample	38	4½

tion, forceps delivery was attempted in six of the patients [R.E., H.M., F.D.R., M.M.(2), S.K., L.C.]. There was one instance of a tight contraction ring noted in this group (F.D.R.). There were five fetal deaths [S.F., R.E., M.M.(1), F.D.R., and S.K.] and one maternal death (F.D.R.).

There were two cases of maternal distress (F.M., and J.S.) both of which resulted in dead babies (Table II).

Fetal distress without an associated prolapsed cord was the indication for the termination of labor in two cases (G.C., and J.C.) and one dead baby resulted (G.C.) (Table III).

In eight cases there was a prolapse of the cord (Table IV). The membranes were ruptured artificially in two cases [M.S.(2) and V.R.] and spontaneously in six (S.P., T.D., A.M., K.T., E.T., and J.N.). The cervix was fully dilated in both cases of artificial rupture and one stillbirth resulted [M.S.(2)]. Where spontaneous rupture of the membranes occurred with prolapse of the cord, the cervix was fully dilated in three cases, 4½ fingers dilated in one, 4 fingers in one and 2½ fingers in one. Four fetal deaths resulted in this group [M.S.(2), A.M., E.T., and J.N.] as well as one maternal death (A.M.).

Results of Version and Breech Extraction

In summary, there were nine babies born dead and three died shortly after delivery, a total of twelve disastrous results or an uncorrected fetal mortality of 57.1 per cent. In all instances except four, the fetal heart was good up until the time of delivery. In one [M.M.(1)], the fetal heart was lost sixteen hours before delivery. In the second (G.C.),

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INTRAPARTUM COURSE	POST-PARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
Head floating. Membranes ruptured when cervix was almost completely dilated. Unsuccessful attempt with Tarnier forceps. Version and breech extraction performed. Manual removal of placenta, hemorrhage, shock	Morbid 100.4 scale	8 lb. 12½ oz.	Living	
After being in labor 2 hr. membrane ruptured spont. Vaginal examination revealed cervix to be 4 F. dilated but fully dilatable. Head floating in L.O.T. with ant. parietal present. After making no progress for 1½ hr. high Barton forceps applied but no progress with traction. Version and breech extraction performed. F.H. good until delivery	Non-morbid	9 lb. 4 oz.	S.B.	(1) Tentorial tear (2) Subtentorial hemorrhage (3) Subarachnoid and subdural hemorrhages (4) Laceration of vein of Galen (5) Subdural hemorrhage of cord
When cervix became 4 F. dilated, membranes were artificially ruptured. Head high. Following rupture of membranes cervix was only 3 F. dilated and pains became poor. When cervix became fully dilated, Kielland forceps attempted unsuccessfully. Version and breech extraction performed successfully	Non-morbid	7 lb. 1 oz.	Living	
Admitted with history of having been in labor 36 hr. Uterine inertia. Two hours after admission cervix found to be fully dilated with head floating. Membranes ruptured artificially. Given 3 minims pituitrin after 4 hr. with no progress. Version and breech extraction performed with difficulty	Morbid 101 scale	8 lb. 9½ oz.	Living Fract. of clavicle	

there was evidence of fetal distress by an irregular and slow heart prior to delivery. In the third [M.S.(2)] there was a prolapsed cord with slowing of the fetal heart, while in the fourth case (J.N.) the prolapsed cord was noted as pulsating. In the three latter cases there was an additional factor present, namely, cephalopelvic disproportion. It is felt that in the remaining eight cases the method of delivery was a factor in the production of stillbirths, with a consequent corrected fetal mortality of 38 per cent.

There were two maternal deaths, an incidence of 9.5 per cent. In the case of F.D.R. (Table I) there was secondary uterine inertia present, an attempt at forceps delivery was made, and a contraction ring added to the complications. Delivery was accomplished by a difficult version and breech extraction resulting from a definite cephalopelvic disproportion which was not recognized. After delivery the patient went into shock, and after a morbid postpartum course died on the thirty-first postpartum day from thrombosis of the left pulmonary artery and infarction of her lung. In addition, the postmortem examination revealed a fistula of the bladder, abruption of the bladder from its pubic attachment, multiple foci of suppurative nephritis, and a well-involuting normal postpartum uterus.

Mrs. A.M., who had been under the care of a midwife, was admitted to the hospital in active labor. The vertex was unengaged, the cervix 4½ fingers dilated, the membranes were ruptured for an unknown length of time, and the cord was prolapsed but pulsating. The fetal heart was good, a version was attempted and a contraction ring noted. Under ether anesthesia and adrenalin, the contraction ring was partially relieved and a version performed easily. Breech extraction followed, with difficulty in delivery of shoulders, and a stillbirth

TABLE II.

NO.	NAME	YEAR	AGE	RACE	PARITY	WT. OF PREV. BABIES (LB.)	POSI- TION	PELVIS	FIRST STAGE (HR.)	SECOND STAGE (HR.)
1	F. M.	1944	39	White	2	7 $\frac{1}{4}$	L.O.T. with asyncl.	Clinically ample	6	2
2	J. S.	1937	26	White	2	1-7 $\frac{1}{2}$ 2-Un- known	R.O.T.	Clinically ample. P.P. x-ray: platypel- loid pelvis A.P. -9.4 T. -12.3	14 $\frac{3}{4}$	2

TABLE III. FETAL DISTRESS WITHOUT

NO.	NAME	YEAR	AGE	RACE	PARITY	WT. OF PREV. BABIES	POSI- TION	PELVIS	FIRST STAGE (HR.)	SECOND STAGE (HR.)
1	G. C.	1934	39	Negro	2	Unknown	L.O.A.	Diag. Cong. 11.25, P.P. x-ray: small android pelvis A.P. -9.8 T. -10	36	1
2	J. C.	1937	37	White	6	7 $\frac{1}{4}$ to 12 lb.	R.O.T.	Clinically ample	7	1

MATERNAL DISTRESS

INTRAPARTUM COURSE	POST-PARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
Fibromyoma uterus. Hypertension. Head floating in L.O.T. position with posterior async. After 6 hr. cervix was thought to be fully dilated on rectal examination with an unengaged head. Membranes ruptured spontaneously. Despite good pains there was no progress. After 1½ hr. general condition became poor with rapid pulse and prostration. Version performed with difficulty and Piper forceps employed for the aftercoming head. Mother aspirated vomitus, became cyanotic and for several minutes condition was grave. F.H. good at time of delivery. Cephalopelvic disproportion	Morbid 100° scale	9 lb. 13½ oz.	S.B.	Intracranial birth injury
Floating head. When cervix became fully dilated, membranes were artificially ruptured. After 1 hr. in second stage with vertex still unengaged, patient showed evidence of maternal distress: falling B.P. and rapid pulse. Kielland forceps applied unsuccessfully. Version and breech extraction performed with difficulty in delivery of aftercoming head. Piper forceps unsuccessfully applied. Cervix lacerated. P.P. hemorrhage—1,000 c.c., shock. Cephalopelvic disproportion—maternal distress (patient delivered by cesarean section with next pregnancy)	Nonmorbid	9 lb. 8 oz.	Died within 1 hour	(1) Subdural hemorrhage (2) Lac. of tentorium cerebelli (3) Fract. of occipital bone (4) Aspiration of infected amniotic fluid

AN ASSOCIATED PROLAPSED CORD

INTRAPARTUM COURSE	POSTPARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
Vertex was in L.O.A. position and remained floating throughout first stage of labor. After being in labor 32 hr. F.H. became slow and irregular. Cervix was thought to be fully dilated and membranes were artificially ruptured. Following this, cervix was found to be only 4 fingers and thick. F.H. continued to be slow and irregular.	Morbid 100° scale	7 lb.	S.B.	P.M. was not obtained
After 36 hr. of labor, cervix was dilated manually to full dilatation. In attempting to perform version, contraction ring was encountered which failed to disappear under ether anesthesia. High Kielland forceps was attempted unsuccessfully. Patient was given 10 minim of adrenalin, after which version and breech extraction were performed with difficulty. Fetal distress and cephalopelvic disproportion				
Vertex floating in R.O.T. position. After 6 hr. of labor, F.H. became irregular. Cervix was 4½ fingers dilated. One hour later cervix was fully dilated. Membranes were artificially ruptured and version and breech extraction performed	Nonmorbid	9 lb. 9 oz.	Living	

TABLE IV.

NO.	NAME	YEAR	AGE	RACE	PARITY	WT. OF PREV. BABIES	POSI- TION	PELVIS	FIRST STAGE	SECOND STAGE
1	M. S. (2)	1943	26	Negro	5	8 lb. 5 oz. 8 lb. 7 lb. 6 oz. 8 lb. 8 lb. 10 oz.	R.O.T.	Clinically ample	Combined 5½ hr.	
2	V. R.	1934	28	White	2	5½ lb. 9 lb.	R.O.P.	Clinically ample	6¾ hr.	15 min.
3	S. P.	1933	43	White	9	7 to 8 lb.	R.O.A.	Clinically ample	8½ hr.	30 min.
4	T. D.	1936	48	White	8	7 to 7½ lb.	L.O.A.	Clinically ample	Combined 7 hr.	
5	A. M.	1934	41	White	4	6 to 8 lb.	R.O.A. Comp'd with hands and feet	Clinically ample	Combined 6 hr.	
6	K. T.	1934	31	White	3	11 lb. (home) 7 lb. 7 lb.	L.O.A.	Clinically ample	4 hr.	45 min.

PROLAPSED CORD

INTRAPARTUM COURSE	POST-PARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
Patient was transferred from another hospital with cervix fully dilated and in moderately severe pre-eclampsia. Vertex was floating in R.O.T. position. Membranes were artificially ruptured with prolapse of small loop of pulsating cord. Cord was replaced and F.H. was heard beating 80-100 per min. Version and breech extraction performed with difficulty. Fetal distress and cephalopelvic disproportion were present	Morbid 100° scale	10 lb. 13 oz.	Died after 6 hours	(1) Fracture of cervical vertebrae (2) Incomplete laceration of spinal cord (3) Subdural, sub-arachnoid and intraventricular hemorrhages (4) Hem. into mediastinum (5) Hem. into lungs with aspiration
Vertex was floating and cervix was fully dilated when membranes were artificially ruptured. Cord prolapsed and reposition was unsuccessful. Version and breech extraction performed with no difficulty	Nonmorbid	7 lb.	Living	
Vertex floating and cervix thick and 2½ fingers dilated when membranes ruptured spontaneously with prolapse of cord. F.H. remained between 60-100 min. for next 1½ hr. until cervix became fully dilated. Version and breech extraction performed	Nonmorbid	8 lb.	Living. Depressed fracture of skull and Erb's Palsy of right arm	
After being in labor 6½ hr., membranes ruptured spontaneously with cervix dilated 4 fingers. Cord prolapsed. By time patient was ready for delivery, cervix was fully dilated. Version and breech extraction performed	Morbid 100° scale	7 lb. 5 oz.	Living	
Patient was under care of midwife and was admitted to hospital in active labor. Vertex was unengaged, cervix 4½ fingers dilated, membranes were ruptured for an unknown length of time, and cord was prolapsed but pulsating. Fetal heart was good, version was attempted and contraction ring noted. Under ether anesthesia and adrenalin, contraction ring was partially relieved and version performed easily. Breech extraction followed, with difficulty in delivery of shoulders, and stillbirth resulted. Two thousand c.c. blood loss was sustained, cervix was lacerated, and death followed in four hours	Maternal death	7 lb. 8 oz.	S.B.	P.M. not obtained
Membranes ruptured spontaneously with prolapse of cord while patient was receiving enema. Vaginal examination revealed vertex floating in L.O.A. position and cervix fully dilated. F.H. was good. Version and breech extraction easily performed	Morbid	6 lb. 3 oz.	Living	

TABLE IV

NO.	NAME	YEAR	AGE	RACE	PARITY	WT. OF PREV. BABIES	POSITION	PELVIS	FIRST STAGE	STAGE SECOND
7	E. T.	1935	31	White	5	12½ lb. 11 lb. 10 lb. 9½ lb. 8½ lb.	R.O.P.	Clinically ample	2 hr.	1 hr.
8	J. N.	1936	25	White	1	Unknown	L.O.A.	Clinically ample P.P. x-ray: Pla- typelloid A.P. -9.2 T. -14.6	6½ hr.	15 min.

resulted. Two thousand cubic centimeters blood loss was sustained, the cervix was lacerated and death followed in four hours. A postmortem examination was denied but it was the consensus of opinion that the patient had a ruptured uterus from an extension of the cervical laceration.

Discussion

Although this series is not large, there are significant facts which must not be overlooked; namely, a corrected fetal mortality of 38 per cent and a maternal mortality of 9.5 per cent. Careful scrutiny reveals the fact that version and breech extraction per se cannot be condemned, because in 9, or 42.9 per cent, of the cases in which no other complications existed, satisfactory results were obtained. There is a tendency, however, to perform version and breech extraction without a thorough investigation of the causes for the persistent lack of engagement, which factors may act as contraindications for this procedure.

In this series, it was found that in the twelve cases with disastrous results, six patients had cephalopelvic disproportion. Although in three of these six cases there were also evidences of fetal distress, it was felt that cephalopelvic disproportion contributed toward this distress [G.C., M.S.(2), and J.N.]. Furthermore, delivery by version and breech extraction was accomplished with difficulty and resulted in stillbirths in which definite evidences of birth injuries were found. Unfortunately, an accurate appraisal of the size of the baby by clinical means is not always easy, especially in a multipara with an obese, pendulous abdominal wall. In addition, one usually seems less concerned in this type of patient after obtaining a history of spontaneous deliveries of moderately large babies. However, in those instances in which successive pregnancies are associated with progressively larger babies, the point may finally

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INTRAPARTUM COURSE	POST-PARTUM COURSE	WEIGHT OF BABY	RESULT (BABY)	POSTMORTEM FINDINGS
Vertex floating. Membranes ruptured spontaneously with prolapse of cord. Cervix was fully dilated. Version and breech extraction performed with difficulty due to extended arms. Piper forceps used for aftercoming head. F.H. was good until time of delivery	Nonmorbid	8 lb. 12 oz.	S.B.	(1) Multiple sub-pleural hemorrhages (2) Multiple sub-capsular hem. of liver (3) Hem. into right adrenal (4) Aspiration of amniotic fluid and meconium
After being in labor 6 hr., membranes ruptured spontaneously with prolapse of pulsating cord. By time patient was prepared for delivery, cervix was fully dilated with vertex floating. Version and breech extraction performed with difficulty with aftercoming head. Piper forceps used. Fetal distress (?) and cephalopelvic disproportion	Morbid 101° scale, P.P. psychosis	7 lb. 10 oz.	S.B.	(1) Tear of tentorium cerebelli (2) Subdural and subarachnoid hemorrhage

be reached when a baby may be too large to come through a pelvis which apparently was adequate for previous passengers. A very accurate study of the pelvis by other than clinical means in the average multipara is infrequently obtained if the patient was capable of delivering previous offspring either spontaneously or with a minimum of difficulty. Yet, she may possess a pelvis which is normal or distorted and moderately contracted, and which, while adequate before and apparently clinically ample, may account for a serious disproportion with only a moderate increase in the size of the present passenger. It should be stressed that in a multipara with a persistently unengaged vertex, one should exclude the presence of cephalopelvic disproportion before attempting version and breech extraction. If this cannot be determined by clinical means, stereoroentgenograms may be employed.

The persistent presence of a rim of cervix in the multipara with an unengaged head and ruptured membranes is not unusual and the judgment as to how negotiable such a rim may be for the safe delivery of the baby by version and breech extraction requires a nicety of judgment on the part of the operator. There were four cases in which the cervix was considered to be negotiable but in which difficulty was encountered in the performance of version and breech extraction, with resulting stillbirths and one maternal death. Possibly, if the version had been performed and the breech extraction delayed until the cervix had become fully dilated, results in this group might have been more favorable. At any rate, the maternal death could have been prevented.

Neglect in labor in the multipara unfortunately is not uncommon because of the laissez-faire attitude of the obstetrician toward this type of patient. There were 10 cases in this series in which there was a prolonged second stage

which varied from $1\frac{3}{4}$ to $7\frac{1}{2}$ hours, with a cervix considered to be fully dilated or fully dilatable. It is the attitude of this obstetric service, in more recent years, in order to prevent neglect in labor to intervene or at least investigate thoroughly the multipara with an unengaged head after a second stage of thirty minutes without progress.

During the ten-year period from 1933 to 1943 there were 22 cesarean sections performed after the onset of labor on multiparous patients in whom there was persistent lack of engagement of the vertex and in whom cephalopelvic disproportion was appreciated early in labor. One fetal death resulted from birth injuries (intracranial hemorrhage and tear of the falx cerebri) after a $9\frac{1}{2}$ -hour labor with $5\frac{1}{2}$ hours of ruptured membranes. There were no maternal deaths in this group.

Conclusions

1. Version and breech extraction for the unengaged head in the multipara was associated with a corrected fetal mortality of 38 per cent and a maternal mortality of 9.5 per cent.

2. The failure to recognize cephalopelvic disproportion accounted for 50 per cent of the fetal deaths. In the presence of failure of engagement in the multipara, therefore, version and breech extraction should not be performed unless there is absolute proof that no disproportion exists.

3. The presence of a residual rim of cervix may be a very definite hazard in the performance of a version and breech extraction. Version may be safely executed but the breech extraction deferred until the cervix offers no obstruction.

4. Upon recognition of cephalopelvic disproportion, cesarean section is the procedure of choice. In twenty-two such cases there was but one fetal death (4.5 per cent) and no maternal deaths.

DELIVERY AFTER CESAREAN SECTION

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THE method of terminating pregnancy following cesarean section is still a controversial matter in the present-day practice of obstetrics. Numerous articles have been published favoring or discrediting the famous dictum "once a cesarean, always a cesarean." There have been relatively few series of cases of pregnancy following cesarean section published, especially in the English literature, to illustrate the truth or fallacy of such a statement. At this time we do not wish to present any additional argument on the subject, but merely to record the outcome of all viable pregnancies which have been delivered in the Woman's Clinic of the New York Hospital following a previous cesarean section. This study covers a twelve-year period from Sept. 1, 1932, to Dec. 31, 1943, and consists of 445 viable pregnancies following a previous section.

In this clinic, each pregnancy following cesarean section is carefully evaluated as an individual problem. The patients are referred to the Dystocia Clinic where they are followed in the latter weeks of their pregnancy by one of the senior physicians. By this time, abstracts of their previous history have been obtained, so that in the great majority of cases the indications for the previous section, and the course of the puerperium are known. Each patient is carefully examined to determine pelvic measurements, approximate size and position of the fetus, and the condition of the scar. Admittedly, examination of the scar is unsatisfactory in the majority of cases, but, in a few, the defect could be palpated through the diastasis of the abdominal muscles. All cases of previous disproportion or relative disproportion are x-rayed, and the measurements and morphology of the pelvis are determined by isometric and stereoscopic methods. Patients are instructed to report any abdominal pain or soreness, and to enter the hospital before their expected date of confinement to await the onset of labor. If labor begins or the membranes rupture before admission, they are to report immediately. In the hospital, they are again re-evaluated by the attending staff. If an elective section is not done, labor is carefully observed and close attention focused on tenderness over the scar, pulse, and fetal heart rate.

Listed in Table I are the indications for the original section in the entire series. In approximately 25 per cent of the cases (112) the original section was performed in this clinic; the other three-fourths were performed elsewhere and came here for a subsequent pregnancy. The indications, in general, are the same in both groups. In our own cases, we have a smaller percentage of patients with disproportion or relative disproportion, and a somewhat greater number of patients with placenta previa and premature separation of the

TABLE I. INDICATIONS FOR ORIGINAL SECTIONS

	TOTAL CASES	SECTION N.Y.H.
Disproportion	253	55
Relative disproportion (i.e., disp. with breech, hydroceph., x-ray disp., unengaged vertex after 12-hour trial of labor)	26	5
Defective powers of labor (i.e., weak uterine scar, desultory labor, cervical dystocia, constriction ring)	30	4
Premature separation of placenta	23	15
Placenta previa	38	11
Abnormal presentation	15	6
Severe pre-eclampsia or eclampsia	20	6
Obstruction to soft parts (i.e., cysts, vesicovaginal fistula)	4	1
Fetal distress (i.e., prolapsed cord, maternal disease)	3	2
Elderly primigravida	3	2
Miscellaneous	7	3
Unknown	15	0

TABLE II. TYPE OF PREVIOUS SECTION

Classical	169
Cervical	141
Extraperitoneal (Latzko)	21
Peritoneal exelusion	1
Total	332

TABLE III. TYPE OF DELIVERY AFTER PREVIOUS SECTION

Cesarean section	257	(58%)
Classical	165	
Cervical	87	
With hysterectomy	5	
Vaginal, operative	98	(22%)
Low forceps	65	
Midforceps	17	
Breech extraction	8	
Other	8	
Vaginal, spontaneous	90	(20%)

placenta. The type of previous section was known in 332 patients, as shown by Table II. In patients with more than one section, that occurring just prior to the present pregnancy is the one recorded.

Table III shows the type of delivery which occurred after cesarean section. Fifty-eight per cent of the patients were delivered by another section. About two-thirds of these were classical sections, and one-third, low flap. There were five sections with hysterectomy because of ruptured uteri. Forty-two per cent of the patients were delivered vaginally. Slightly more than one-half of the vaginal deliveries were operative, and the remainder spontaneous.

Among those patients delivered by repeated section, there are several points of interest. As would be expected, disproportion was the most frequent indication for repeated section (Table IV). A large proportion, 25.8 per cent, were indicated because of a defective uterine scar or febrile puerperium. There was a high incidence of premature separation of the placenta and placenta previa which occurred in this group of patients requiring another section, the incidence being 2.5 per cent as compared to the clinic incidence of 0.84 per

TABLE IV. INDICATIONS FOR SECTION AFTER PREVIOUS SECTION

Disproportion	140
Previous section with fever or defective scar	66
Relative disproportion	7
Previous section	14
Premature separation	4
Placenta previa	7
Abnormal presentation	5
Severe pre-eclampsia	2
Obstruction to soft parts	2
Elderly primigravida with previous section	3
Fetal distress	2
Maternal disease	1
Miscellaneous	4
Total	257

cent. One patient had cesarean sections for premature separation of the placenta on two occasions, and two cases of placenta previa had a repeat section for the same indication.

(In cases of vaginal delivery, a routine low forceps is considered the procedure of choice after a previous section. In many cases this procedure was not followed, and in others low forcep deliveries were performed for other indications, as shown in Table V.

TABLE V. INDICATIONS FOR OPERATIVE VAGINAL DELIVERY AFTER PREVIOUS SECTION

	LOW FOR- CEPS	MID- FOR- CEPS	HIGH FOR- CEPS	BREECH EXTR.	MAN- UAL RE- MOVAL PLA- CENTA	BAG INDUCT.	VER- SION EXTR.	MAN- UAL DILA- TION OF CERVIX
Previous section	51	10						
Prolonged 2nd stage	2	2						
Lack of progress in 2nd stage	3	1						
Fetal distress	7	1	1					
Breech				8				
Retained placenta					2			
Maternal distress		2				1		
Mild pre-eclampsia	1							
Transverse presentation (1 twin)							2	
Severe pre-eclampsia						1		
Pulmonary tuberculosis	1							
Intrauterine infection		1						
Cervical stenosis								1

The most marked variation in incidence of vaginal deliveries following cesarean section is found in the group where previous section was performed for the indication of disproportion, as compared to that group in which disproportion or relative disproportion did not enter into the original indication. Of 253 previous sections for disproportion, 78, or 31.7 per cent, had a vaginal delivery at this time. Among 80 of these patients who had had two sections for disproportion, 12 were judged capable of vaginal delivery and went through labor without incident. In contrast to this group are the patients who had previous sections for severe pre-eclampsia, abnormal presentations, desultory labor, and other abnormalities which are not likely to be present in succeeding

pregnaneies. This group should represent the greatest possible percentage of patients with vaginal deliveries after section. Among 124 of these patients, 73, or 58.9 per cent, delivered vaginally, the remainder by repeated section.

The more cesarean sections a patient has had, the less chance there is for vaginal delivery to occur in a following pregnancy, and the more vaginal deliveries a patient has had, particularly following a cesarean section, the greater is the probability of vaginal delivery. This is well shown in Table VI.

TABLE VI. TYPES OF DELIVERY AMONG PATIENTS WITH PREVIOUS SECTION

	REPEAT SECTION	VAGINAL DELIVERY
No. with previous section only (315)		
248 one section	148	100
52 two sections	40	12
9 three sections	9	0
5 four sections	4	1
1 five sections	1	0
No. with vaginal delivery prior to section (85)	45	40
No. with vaginal delivery following section (45)		
34 one vaginal delivery	4	30
8 two vaginal deliveries	2	6
2 three vaginal deliveries	0	2
1 seven vaginal deliveries	0	1

Of 85 patients who had vaginal delivery prior to section, 40, or 47.1 per cent, were delivered vaginally after section. However, among patients who had a vaginal delivery following cesarean section, 86.6 per cent again delivered per vaginam. One patient had as many as eight vaginal deliveries following a previous section. Theoretically, the entire group should have delivered normally, but in six, added complications, such as placenta previa, premature separation of the placenta, and abnormal presentation made a repeated section necessary. Section was performed in four patients with one intervening vaginal delivery, and in two with two vaginal deliveries after a previous section. There were 248 patients in this series whose only previous pregnancy had been terminated by cesarean section. In a second pregnancy, a repeated section was performed in 148 cases (58.8 per cent) while 100 (40.3 per cent) delivered vaginally. Fifty-two patients had two previous sections and, among these, only 12 (23.1 per cent) delivered vaginally. The greatest number of sections performed on one patient was six.

In general, it is our policy to sterilize a patient at the time of her third cesarean section. With multiple scars in the uterus, pregnancy is thought to become increasingly hazardous. Sterilization was performed in 67 cases, generally by the Madlener or Pomeroy technique. We have not had any of these patients return, but one patient, who had been sterilized elsewhere, returned here for delivery. Among the 67 sterilization operations at the time of section, 56 patients had three or more living children. Eleven had only two children, but in these cases other indications were also present, such as rheumatic heart disease, hypertension, and marked defects in the uterine scar.

Though there are a large number of patients who have a repeated cesarean section, not all of these have elective operations, but many are given a trial of

labor. Of 253 repeat sections, 76.3 per cent were elective, and the remainder were allowed to go into labor. The average trial of labor lasted 10 hours and 48 minutes. In general, the decision as to whether or not a section was necessary was made before 18 hours of labor. However, there were two cases with a prolonged trial of labor of 40 and 60 hours, after which section became necessary.

The labor of patients having vaginal delivery following a previous section has recently been reviewed by Kúder and Dotter from this clinic. Among patients who had no previous vaginal delivery, labor following cesarean section was similar to that of a primigravida, and lasted an average of 17 hours and 58 minutes. Among patients who had a previous vaginal delivery, labor followed closely the pattern of multiparous labor and lasted an average of 10 hours and 48 minutes. The incidence of prolonged labor, or those of over 30 hours' duration, is 7.5 per cent, and that of precipitate labor of three hours or less is 3.2 per cent; this compares with the clinic incidence of prolonged and precipitate labor which is 9.5 per cent and 6.1 per cent respectively.

TABLE VII. PRESENTATION

	PREVIOUS SECTION PATIENTS NO.	PER CENT	GENERAL CLINIC PER CENT
Vertex	399	91.5	95.0
Transverse	8	1.83	0.09
Face	3	0.66	0.27
Breech	26	5.96	4.0
Twins (not included)	4		
Unknown	4		

As shown in Table VII, there is an unusually high incidence of abnormal presentation among these patients which may be explained on the basis of poor pelvic architecture. Fourteen of the patients with a breech presentation had had a previous section for disproportion, two had previous sections for abnormal presentations (face and chin), and one had a bicornate uterus. The patients with face presentations had all had previous sections for disproportion. Among patients with transverse presentation, one had had two previous sections; and another, one previous section, all of which were again indicated because of transverse presentation. One of these also had a pelvic kidney, and the remainder had previous disproportion with sections in earlier pregnancies. Forty-three out of 399 vertex presentations, or 12.4 per cent, were in the posterior position as compared with the usual clinic incidence of 7.9 per cent.

As one might expect, the pelvic measurements among patients with previous section are remarkable only among those in whom the indication for section was disproportion. In this clinic a pelvis with a diagonal conjugate of 11.7 cm. or below, or an intertuberos diameter of 8.5 cm. or less, is considered contracted and likely to cause dystocia. Fifty-two patients out of 253 who had a past history of disproportion had pelvic measurements which were considered within normal limits. However, the general average for the entire group with disproportion as a previous indication for section was 11.3 cm. for the diagonal conjugate, and 8.8 cm. for the intertuberos diameter. There were

only seven with a diagonal conjugate of 10 cm. or below. The smallest pelvis had a conjugate of 7.5 cm. and a transverse inlet diameter of 7 centimeters.

During recent years, the x-ray has been used more and more frequently as a check on clinical pelvic measurements. In the past, x-ray diagnosis of cephalopelvic disproportion has been notably unreliable, and has undoubtedly been considerably abused. Even now, with accepted methods of pelvimetry, mistakes in judgment are made. There were four patients in this series who had previous sections for disproportion which were based, to a large extent, on x-ray findings. At least one of these patients had an accepted type of x-ray pelvimetry; but when an x-ray series was repeated here, our interpretation was not in accord with the former one and she had an uneventful vaginal delivery.

In this clinic, x-ray interpretation and diagnosis is made by an obstetrician on the staff who, however, has had no contact with the patient whose x-ray he is interpreting. Up to the present time, we have not allowed our clinical judgment to be influenced by his opinion, but use it rather as corroborative evidence of what we find after clinical evaluation. We use the Caldwell and Moloy stereoscopic technique which, in turn, is checked by isometric pelvimetry as developed by Steele and Javert of this clinic. As previously stated, part of our routine check on patients with previous section for any questionable disproportion consists of pelvic x-rays. It should be remembered that x-ray evaluation of these patients is made without any knowledge of their previous obstetric history.

The x-ray had not been used extensively in this clinic until the past four or five years, and, consequently, there are only 92 patients with a previous history of disproportion on whom we have secured x-ray data concerning the type of pelvis or prognosis as to method of delivery.

TABLE VIII. X-RAY DIAGNOSIS IN PATIENTS WHO HAD PREVIOUS SECTION ON BASIS OF DISPROPORTION

Elective section	21
Probable section	14
Possible section	21
Vaginal delivery with transverse arrest	8
Vaginal delivery without difficulty	28
Total	92

As shown in Table VIII, in 64 out of 92 cases, trouble was predicted after an x-ray study of the pelvis. In 21 patients, elective section was dogmatically advised. Almost invariably these patients had unusually poor pelvic measurements, and overriding of the fetal head could be demonstrated clinically. However, a didactic opinion of this type is rare. In most cases, the opinion as to probable and possible section are direct interpretation of the x-ray man's description. With statements such as: "poor pelvis, trouble all the way; will need hard long labor," or, "if head engages it may mold through with hard labor," a section was considered "probable." Fourteen cases fell into this

group. With less emphatic statements such as: "advise trial labor," "if vertex engages will deliver vaginally" or "will need good labor to deliver," section was considered "possible"; there were 21 such cases. In 8 patients vaginal delivery was advised, though trouble could be seen in the midpelvis and outlet; in the majority of these transverse arrest was predicted. In 28 cases vaginal delivery or an easy forceps was assured.

TABLE IX. TYPE OF PELVIS IN PATIENTS WHO HAD PREVIOUS SECTION FOR DISPROPORTION

TYPE OF PELVIS	TYPE OF DELIVERY PREDICTED BY X-RAY			
	ELECTIVE SECTION	PROBABLE SECTION	POSSIBLE SECTION	VAGINAL
True Gynecoid	7	6	3	7
Gynecoid-android	1		3	3
Gynecoid-anthropoid	1		2	1
True android	5	2	3	2
Android-gynecoid	2	1	4	3
Android-anthropoid			1	1
Android-platypelloid	2		1	
True anthropoid	1			1
Anthropoid-gynecoid				2
Anthropoid-android		1		
True platypelloid		1	1	1
Platypelloid-gynecoid			1	1

The type of pelvis is described in 71 of these patients (see Table IX). The multiplicity of pelvic forms are described by the classification of the posterior and anterior segments of the inlet into one of the four main morphologic types which they resemble most closely. This group of pelves is too small to permit definite conclusions. It has been shown, however, that in a group of contracted pelves the number of gynecoid forms decreases, while the number of android and flat pelves increases in frequency. The number of flat pelves show no variation from their normal incidence in the present series, but there is a decrease in the number of gynecoid forms and an increase in the number of android types. The gynecoid pelvis is usually found in 56 per cent of patients in the general clinic and the android in 19 per cent. In this series, though, the gynecoid is most frequent (48 per cent), the android type appears about twice as frequently as one would expect in a normal group of pelves (38 per cent).

Another consideration of general interest in patients with previous cesarean section is the appearance of the uterine scar at the time of delivery in a succeeding pregnancy. A description of the scar, or a definite statement that no defect is noted in the uterine wall, should be included in the operative or delivery note of each patient. This information is extremely helpful for the evaluation of future pregnancies. Unfortunately, a definite note of the uterine scar was made in only 168 patients in our series. It is probable that notable defects in nearly all the patients who delivered by section are recorded, for abnormalities are generally well described in the operative notes. Therefore, the number of defects described at the time of cesarean section are more likely the defects represented in the entire series rather than the small group which

we have recorded here. Among the 168 cases where attention was directed to the previous cesarean scar, it was noted in 146 sections and 22 vaginal deliveries.

TABLE X. TYPE OF PREVIOUS SECTION WITH DEFECTIVE SCAR

Classical	40
Cervical	15
Latzko	3
Unknown	6
Total	64

Table X shows the type of previous section in cases with defective scars. From the figures presented in this table, the greatest number of defects noted were in the classical type of cesarean section. However, as we have shown in Table II, the classical section was performed in over half of the patients, and data are too inconclusive for any statement as to whether the type of section per se was a factor in increasing the incidence of uterine defects. Furthermore, a small defect would be more easily detected in the scar of the classical section.

TABLE XI. TYPE OF DELIVERY IN CASES WHERE DEFECT NOTED

Cesarean section	54
Previous section with fever	15
Defective scar	12
Disproportion	20
Previous section	2
Ruptured membranes and floating head	2
Ovarian cyst	1
Placenta previa	1
Premature separation of placenta	1
Operative vaginal delivery	7
Low forceps	3
Midforceps	2
Breech	1
Version-extraction	1
Spontaneous vaginal deliveries	3
Total	64

We have already stated that 25.5 per cent of repeat cesarean sections were performed on the basis of a defective uterine wall, either because of a febrile puerperium or faulty repair of the uterine wound. The indications for operation among patients in whom defects were noted in the previous scar are listed in Table XI. In the 46 sections where some degree of faulty union was observed in the previous scar, 22 were suspected prior to operation. The majority of the sections were indicated on the basis of disproportion; less than one-half were indicated because of a defective scar. The difficulty of evaluating the condition of the uterine scar prior to labor is well illustrated by the 62 patients in whom operation was indicated because of a suspected weak scar. Twenty-two, or about one-third, had uterine defects of all degrees; in 18 the scar was well healed or no defects could be noted; in the remaining 22, no mention was made of the previous scar which may be presumed to be unremarkable. However, the history of a febrile puerperium still remains an im-

portant consideration in evaluating a patient in a succeeding pregnancy, as the uterine defects may be expected in one of three such patients, while the incidence among other patients would appear to be much lower. Nine patients who delivered vaginally were noted at examination after delivery to have uterine defects, but in only one, where a wide thin scar was described, were further vaginal deliveries felt to be contraindicated.

TABLE XII. UTERINE SCAR AS DESCRIBED AT TIME OF REPEAT SECTION

No evidence of previous scar	61
Scar well healed	18
Adhesions but no defect	9
Scar thin	18
Small defect	10
Thin with defect	10
Very thin	13
Ruptured	6

The types of uterine scar, as described at the time of cesarean section, are listed as briefly as possible in Table XII. In the majority of cases (60.3 per cent), the scar was either not identified as such, or was described as well-healed. In cases where the scar is listed as thin or with a small defect, in our opinion, the patient could have withstood labor without danger of rupture. In these patients, the myometrium was somewhat thinner along the scar of the previous section, or there were small depressions (1 to 2 cm.) in the muscularis. There were 23 patients in whom the scar was very thin, or who had large defects in the muscularis. In several of these patients, the uterine wall was described as 1 to 3 mm. thick, and many in this group would undoubtedly have ruptured the scar with good labor. The patients with ruptured uteri will be discussed in detail.

The incidence of ruptured uteri was 1.7 per cent. Pertinent data concerning these cases of ruptured uteri is presented in Table XIII. Rupture occurred

TABLE XIII. PATIENTS WITH RUPTURED UTERI

PARA	TYPE OF PREVIOUS DELIVERY	INDICATION FOR PREVIOUS DELIVERY	FEVER IN PREVIOUS PUERPERIUM (DAYS)	DURATION OF LABOR (PRES. PREGNANCY)	TYPE OF DELIVERY	RUP- TURED SCAR	FETAL MOR- TALITY
I	Cervical	Disproportion	10	Early—1 hr.?	Hysterectomy	Yes	0
I	Classical	Placenta prev.	3	17 hours	Hysterectomy	Yes	1
I	Classical	Prem. separ.	2	Early	Class. section	Yes	0
III	3 Classical	Disproportion	3-2-3	10 hours	Hysterectomy	Yes	1
II	1 Breech ext. 1 Latzko	Chin post.	10	0 "	Low-flap sect.	Yes	0
II	1 Cervical 1 Breech ext.	Face post.	4	17 hours	Hysterectomy	No	1
II	2 Cervical	Disproportion	5	12 hours	? cervical	Yes	1
II	1 Forceps 1 Cervical	Disproportion	3	18 hours	Midforceps Hysterectomy	No	1

three times among those with a previous classical section; three times with a previous low-flap section, once following a Latzko section, and once in a patient where the nature of the previous section was not known, but was believed to be of the cervical type. There is no indication among this group that ruptures occur more frequently following the classical operation, for, as we have already shown, the majority of sections were of this type. In two patients with ruptured uteri, it was very difficult to correlate the rupture with their previous cesarean scar. These cases are reported as follows:

The first case is a 30-year-old para ii, gravida iv, who had a low flap section nine years previously because of a posterior face presentation. Six years previously she had an uneventful breech delivery in this clinic of a 3,900-gram infant. After a normal antepartum course in this present pregnancy, she was admitted in early labor. Twelve hours after moderate and normal labor, the cord prolapsed but was readily replaced. Five hours later, when full dilatation was attained, a midforceps delivery was attempted. Tarnier forceps were applied, but the vertex failed to descend and with continued traction the blades slipped. Vaginal examination revealed a transverse defect in the anterior vaginal wall at the level of the cervicovaginal junction. At laparotomy, a deep and extensive laceration was found to involve nearly the entire vaginal wall extending upward through the cervix and lower uterus. A subtotal hysterectomy was performed. On examination of the uterus there was a laceration extending upward on the left lateral aspect of the uterus for a distance of 4 cm. The scar of the previous section was not detectable.

The second case is a para ii gravida iv, whose first delivery terminated by a difficult forceps and a deadborn infant. Five years ago she had a low flap cesarean section for disproportion. In her present pregnancy she was admitted at term in mild labor. After seven and one-half hours of good labor, the fetal heart was lost and the cervix 8 or 9 cm. dilated. Three hours later, when the cervix was fully dilated, the patient was delivered by midforceps of a 2,550-gram infant. On manual exploration of the uterus, a rupture was felt through the musculature, and the patient's blood pressure began to fall. At laparotomy, a large hematoma was noted under the peritoneal reflection of the bladder. Due to the laceration, it was difficult to make out the landmarks, but, starting at the angles of the rupture, an incision was carried posteriorly and the uterus removed. The pathologic description of the gross specimen is as follows:

"As one explores the uterine cavity, there is a fissure in the midline of the anterior wall extending from a point just within the external os to a point running up into the body of the uterus. This may well be the healed scar from the previous section. There is no muscular defect in this area. On bisecting the specimen, there is no evidence of rupture. From gross examination, it seems we are dealing with a rupture of the vagina occurring in the anterior wall beneath the bladder and 2 cm. from the cervix."

In three patients, rupture occurred at the onset of labor, or before the pains were well established; in the remaining five, labor was well established and varied from ten to eighteen hours in duration. One patient failed to come into the hospital at the onset of labor, but remained at home for ten hours, and was admitted in shock. The remaining were observed early in labor when there was no sign of impending rupture. Usually the signs of rupture developed suddenly, with pain, loss of fetal heart, and rising pulse, occurring in sequence or coincidentally. The fetal death rate among these cases was 60 per cent. No fetal death occurred in three patients where rupture occurred early in labor. When rupture occurred later, the fetal mortality was 100 per cent. There were no maternal deaths in this series. We attribute this directly to

close observation, available blood for transfusion, and prompt action. The only patient who went into deep shock had not come to the hospital early, and rupture occurred at home. Hysterectomy was performed in five of the eight cases. In three, the separated scar was freshened and repaired. One of these cases had a tubal ligation; another one has since had another pregnancy which terminated in cesarean section. All of these patients had had a previous febrile puerperium, yet in most the fever was mild; only two patients had fevers of over five days' duration.

TABLE XIV. MORBIDITY, INCIDENCE 29.8 PER CENT

TYPE OF DELIVERY	INCIDENCE %
Spontaneous delivery	6.6
Operative vaginal delivery	17.3
Cesarean section	42.4
Classical	39.4
Cervical	45.9
Section with hysterectomy	66.6

Puerperal morbidity is defined in this clinic as a fever of 38° C. on two or more successive days (and lasting longer than twenty-four hours) excluding the day of delivery. There were very few extragenital causes of fever among the patients in our series, so that in general, postpartum morbidity can be attributed to puerperal sepsis. The incidence of morbidity occurring in this group is 29.8 per cent. This is abnormally high and is accounted for by the large number of cesarean sections performed, which are responsible for 82.6 per cent of the total puerperal morbidity. The morbidity in relationship to the type of delivery is shown by Table XIV. The morbidity following full-term spontaneous deliveries was 6.6 per cent; following operative vaginal deliveries, 17.3 per cent; but following cesarean section, it rose precipitously to 42.4 per cent. The highest morbidity in section cases was associated with the low flap type where the incidence was 45.9 per cent compared with 39.4 per cent with the classical type. The difference can undoubtedly be explained by the fact that 42 per cent of the patients with morbidity and the low flap section had had labor, while only 21 per cent of febrile patients with the classical section had had labor, which averaged shorter in duration. Generally, the febrile reactions were mild, lasting only 2 or 3 days. Only 16 per cent of the total morbidity was caused by fevers lasting over five days.

The high operative morbidity raises the interesting question as to what constitutes the so-called "febrile puerperium" which, in itself, has become an indication for a repeat cesarean section. The proponents and opponents of repeated sections differ most widely on their interpretation of the significance of the previous puerperal course. As indicated here, the morbidity from cesarean section approaches 50 per cent but the percentage of rupture of the scar is relatively low. If the definition of febrile puerperium is strictly adhered to, few patients will have a spontaneous delivery after once having had a section.

TABLE XV. FETAL MORTALITY, 6.9 PER CENT

	NUMBER	WITH SECTION	WITH VAGINAL DELIVERY
Deadborn	18	11	7
Stillborn	2	7	3
Neonatal	10	2	

The fetal mortality rate of all deliveries was 6.9 per cent. Following vaginal delivery it was 5.8 per cent, and after cesarean section, 7.2 per cent. As shown in Table XV, there were 18 deadborn, 2 stillborn, and 10 neonatal deaths. The 11 deadborn infants occurring among cesarean section cases were attributed to asphyxia, caused by premature separation of the placenta, placenta previa, or ruptured uteri. Among the 7 deadborn infants occurring in the vaginal delivery group, 3 deaths were caused by maternal disease (syphilis, erythroblastosis, acute yellow atrophy) 2 from prolapse of the cord, and 2 in which the cause was unknown. Seven of the neonatal deaths which occurred following cesarean section were caused by such conditions as intracranial hemorrhage, erythroblastosis, prematurity, atelectasis, pericardial effusion, and mongolism. Those following vaginal delivery were caused by intracranial hemorrhage and prematurity accompanied by congenital defects.² The stillborn deaths were attributed to asphyxia, though the cause was not clear in either case.

There were three maternal deaths among our series, a mortality rate of 0.67 per cent. They are reported briefly as follows:

CASE 1.—A 40-year-old para ii, gravida iv, who had a section with her first pregnancy because of premature separation of the placenta. This was followed by a full-term spontaneous delivery. She was admitted in the thirty-seventh week of the present pregnancy with acute yellow atrophy of the liver. As soon as the diagnosis was established a bag induction was successfully used, but the patient was moribund during labor and expired shortly afterwards of hepatic failure. This death obviously had no relation to the method of delivery.

CASE 2.—A 40-year-old para ii, gravida iv, who was a mild diabetic, had had a difficult midforceps delivery with her first pregnancy, followed by a classical section in her second pregnancy which was performed on the indication of a large baby. A repeated section was performed with the present pregnancy because the previous puerperal course was not known. Following section, the patient had a postpartum hemorrhage which failed to respond to tamponade of the uterus and shock therapy.

CASE 3.—A 40-year-old para i, gravida ii, whose first pregnancy had been terminated by a Latzko section, the indication being desultory labor and maternal exhaustion. In the present pregnancy she delivered a premature infant spontaneously, but when signs of moderate hemorrhage and profound shock developed postpartum, the uterine cavity was manually explored. She developed signs of intrauterine infection and peritonitis on the following day, and on the twenty-fifth postpartum day died with signs of an overwhelming septicemia, acute endocarditis, and cerebral embolism.

In this case, the shock following delivery seemed somewhat out of proportion to the blood loss and a possible rupture of the uterus was seriously considered. A careful manual exploration of the uterine cavity by three members of the senior staff definitely ruled out this possibility, but may have contributed to the intrauterine infection.

Discussion

Once a patient has had a cesarean section, statistics show that her chances of requiring another section are 58 per cent. This figure is modified somewhat by the original indication for section. If it was for a condition which is not present in the succeeding pregnancy, she has a 58 per cent chance for vaginal delivery. If, however, it was for disproportion, then there is only a 30 per cent chance. However, if she has had a vaginal delivery following a previous cesarean, then the probability of future vaginal deliveries is very much increased. At the same time, the converse is also true that, with more than one section, the chances of repeated section become greater. As we have shown, disproportion is a relative term and does not necessarily mean that it will be present in future pregnancies. There were few patients in whom we could dogmatically predict cesarean section. This point is well demonstrated by the figures on clinical pelvic measurements and x-ray pelvimetry. In most cases disproportion was modified by the powers of labor, position and size of the fetus, and pelvic architecture. It will readily be acknowledged that disproportion itself exerts an influence on the two former factors.

The great problem among patients with a previous section is the condition of the scar and the possibility of rupture. Careful attention should be paid to the scar at the time of operation or vaginal delivery for better evaluation of future pregnancies. We have found it very difficult to secure any knowledge about the scar before delivery. In only one-third of the patients who were operated on for this indication was any defect obvious. Yet in one-half of all defective scars noted, defects were suspected prior to operation. We feel that this is probably as accurate as one can be in the evaluation of the usual patient. A febrile puerperium is important to keep in mind, as all of the cases where rupture occurred had a previous puerperal morbidity. It is well to realize that the infection does not necessarily have to be a severe one, as the majority of the patients had less than five days of a low grade (38° C.) fever. The fact that our morbidity following cesarean section is high (42 per cent) lends support to the opinion of those who advocate "once a section, always a section." The incidence of rupture of the uterus was 1.78 per cent (corrected 1.3 per cent) and is as favorable as any yet reported. The fact that there was no maternal fatality among patients with ruptured uteri was undoubtedly due in great part to careful observation and prompt treatment. Ruptures occurring early in labor had a low fetal mortality while those occurring later carried almost 100 per cent mortality for the fetus.

Conclusions

1. The termination of 445 viable pregnancies following cesarean section are reported.
2. The majority of previous cesarean sections had been of the classical type (57 per cent).
3. Fifty-eight per cent of the patients in this series had a repeat cesarean section. The greatest number of repeat sections occurred in the group where disproportion had been the indication for cesarean section (68 per cent).

Among patients in whom the original indication was no longer present in the succeeding pregnancy, it was lowest (42 per cent).

4. Once a patient had had a vaginal delivery following cesarean section, the greater was the probability of future vaginal deliveries. The converse was also true; the greater number of sections a patient had had, the less the chance of vaginal delivery. The greatest number of vaginal deliveries occurring in one patient following previous section was eight. The greatest number of sections performed on one patient was six.

5. In the majority of sections for disproportion, the indication is relative to the powers of labor, position, and pelvic configuration. This is demonstrated by both clinical and x-ray pelvimetry. For this reason, x-ray pelvimetry can rarely provide an absolute indication for section.

6. An unusually high incidence of abnormal presentations may be explained on the basis of poor pelvic architecture.

7. It is important to examine the scar of the previous cesarean section at the time of operation or vaginal delivery for better evaluation of succeeding pregnancies.

8. Defects in the uterine scar were noted more frequently following the classical type of section.

9. In one-half of the cases where there was a defect in the uterine scar, it was suspected prior to operation. However, in only one-third of the patients in whom section was performed on the indication of damage to the uterine wall, were any defects noted.

10. Rupture of the previous scar occurred in 1.3 per cent of the patients in this series. There were no maternal deaths among these patients; we believe this to be attributed to close observation and prompt action.

11. The high morbidity (29 per cent) is explained by the high operative incidence.

12. The fetal mortality rate was 6.9 per cent.

13. There were three maternal deaths, a mortality rate of 0.67 per cent.

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A COMPARATIVE ANALYSIS OF THE DIAGNOSIS AND TREATMENT OF ENDOMETRIOSIS, INCLUDING A REPORT OF FIFTY-THREE CASES OF INTESTINAL ENDOMETRIOSIS*

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IN A RECENT comparative study of the case records of patients operated upon for endometriosis by the entire staff of Presbyterian Hospital, with particular emphasis on those lesions involving the bowel, certain changes in general diagnosis and treatment were found that seemed of interest. These changes were noted by comparing the two previously reported^{1, 2} groups numbering 569 patients with a more recent group of 317 individuals operated upon by the same surgeons during the last four years.

A definite yearly increase in the proportional number of cases operated upon has occurred (Table I). The rather sharp increase in incidence between the first and second studies was most probably due to the final acceptance of endometriosis as a major gynecologic entity, and the establishment of more accurate diagnostic procedures. This applies both to the resident as well as the attending staff. It was quite apparent at this time that all of us were becoming "endometriosis conscious." The increase in details of diagnostic importance in both the hospital and office records during this period is quite striking. Some of these patients have been operated upon almost entirely on the basis of an intelligent, carefully taken clinical history, without the usual palpatory pelvic findings being clear. The points in the history that seem to be of particular importance in this connection are often not voluntarily given by the patient unless the examiner elicits them by careful questioning (Table II). We refer particularly to the following symptoms:

1. Dyspareunia.
2. Pain in the rectum caused by passage of stool or gas. This pain is usually present only at menstrual time or at least intensified at that time.
3. Recurrent diarrhea coincident with the menstrual period (superficial bowel implants).
4. Symptoms of low grade bowel obstruction, such as nausea, cramplike pains, and constipation at period time (implants involving bowel muscularis or mucosa).
5. Unexplained sterility.
6. Extension of menstrual backache to the thigh and often lower leg.
7. Abnormally increased bladder irritability at menstrual time.
8. Low deep pelvic discomfort caused by jarring of the body, such as walking or riding in an automobile (Counselers³).
9. A history of an acquired dysmenorrhea appearing in a multipara or a change in the type of pain of the functional dysmenorrhea of the nullipara.

*Part of a symposium on Endometriosis before the Chicago Gynecological Society, May 19, 1944.

TABLE I

	ALLEN 1921-1933	HAYDON 1934-1940	THIERSTEIN AND ALLEN 1940-1944
Number of cases	112	457	317
Incidence	8.4%	13.1%	-----
Ovarian function retained	90—88%	296—64%	260—82%
Hysterectomy			
Abdominal	82—73%	134 } 78%	75 } 63%
Vaginal	-----	225 }	125 }
Resections	41	223	150
Mortality	1	0	0
Reoperation	6	0	3

TABLE II

	ALLEN 1921-1933	HAYDON 1934-1940	THIERSTEIN AND ALLEN 1941-1944
<i>Symptoms</i>			
Increased bleeding	79	422	216
Backache	48	179	88
Dysmenorrhea	48	226	114
Abdominal pain	25	70	27
Dyspareunia		70	27
Bowel pain	8	25	33
<i>Associated Lesions</i>			
Fibromyoma	46—41%	253—55%	133—42%
Others	--	243	97
Retroversion	---	81	62

10. Appearance of the symptom-complex or palpatory findings resembling those of pelvic infection in a patient over 35 years of age, since pelvic infection becomes progressively rarer during this decade of life.

11. Finding of blood in the stool at menstrual time which cannot be accounted for by the more common forms of rectal pathology.

The routine employment of combined rectovaginal examination of the pelvis has undoubtedly been responsible for more accurate diagnosis than any other item in our armamentarium.

Palpation by the rectal finger of a single tender nodule in the cul-de-sac may be the key which will unlock the door of diagnosis of many complicated pelvic problems. This fact is especially true if, in subsequent examination at the time of menstruation, a significant increase in tenderness or size of the identifying nodulation has occurred. For this reason, in our experience, it has been more satisfactory to conduct this examination in the unanesthetized patient. Exquisite "point tenderness" will often direct the examiner's attention to a minute nodule which would be overlooked in the anesthetized patient. If, on esthetic grounds, the patient or the doctor objects to an examination during the menstrual period, the day preceeding the onset of the menstrual period seems to be preferable to the postmenstruum. The swelling and tenderness of the lesions is more marked during the period of congestion than during its regression. Preparation by a cleansing enema given the night before and repeated the morning of the examination has materially increased the ease and accuracy of palpation. In fact, this method of examination may materially change the

choice of surgical approach and preoperative prognosis in such conditions as fibroids, ovarian cyst, or retroversion of the uterus which so commonly complicate endometriosis.

Included in this series are a large number of patients who have been operated upon elsewhere for lower abdominal pain or intractable dysmenorrhea without relief. Endometrial lesions of varying extent have been overlooked or misinterpreted. The previous preoperative diagnosis in these patients has ranged from acute or chronic appendicitis, blood cysts of the ovary, retroversion of the uterus, hemorrhoids, pelvic inflammatory disease, uncomplicated fibromyomas, to stenosis of the cervix. Twenty-seven per cent of those patients with endometriosis of the bowel had had appendectomies within the last five years, and, of these, 60 per cent had no relief from recurrent attacks of lower abdominal pain. Two patients had surgical procedures for hemorrhoids with no relief of rectal pain.

Every effort should be made to give endometriosis its proper place in the diagnostic armament of the general surgeon, internist, endocrinologist, urologist, and physician in general practice.

Endometriosis is a progressive, adhesive, penetrating lesion and may require much more destructive surgery, such as castration, than that necessary in myomectomy, suspension of the uterus, resection of ovarian cysts, or even complete hysterectomy for fibromyomas (Table III).

TABLE III

	ALLEN 1921-1933	HAYDON 1934-1940	THIERSTEIN AND ALLEN 1941-1944
<i>Location of Lesions</i>			
Ovaries	60	345	162
Uterus	53	313	142
Cul-de-sac	--	191	80
Ligaments	--	69	89
Bowel	4	22	22
Peritoneum	16	--	19
Tubes	--	16	12
Bladder	3	3	1
Appendix	1	1	2
Vagina	-	-	1
Abdominal	3	3	1
Rectovaginal septum	37	-	16

The widespread distribution of the lesions of endometriosis coupled to their infiltrating propensities may make preoperative prognosis very hazardous. Comparatively small endometrial lesions intimately involving adjacent important structures, such as the rectum, bladder, or ureters, may indicate removal of the ovaries rather than the lesions themselves. However, the loss of only one patient in a group of 886 patients may indicate that we have been too radical in castration and too conservative in resecting lesions involving the bowel.

We do not believe, from a postoperative study of those patients in whom ovarian function has been retained and who are now free of symptoms, that definite conclusions can be drawn concerning the need for total excision of widespread nodules of endometriosis. Many of these patients are symptom-free, and

some have conceived and borne children, although they still have definite endometrial islands left in the pelvis. It is our impression, therefore, that at least in young women desirous of pregnancy, a supreme effort should be made to conserve ovarian function, although only partial removal of the endometrial tissue may be possible. (Table IV). Subsequent x-ray castration is usually accepted more gracefully by the patient if symptoms should persist or recur than is primary institution of the surgical menopause.

TABLE IV

	ALLEN 1921-1933	HAYDON 1934-1940	THIERSTEIN AND ALLEN 1940-1944
Fertility—Taken from histories with adequate marital data			
Number of cases	88	262	185
Sterility			
Absolute	53—60%	168—63%	113—61%
Relative	18	134	--
Number of known pregnancies following operation	8 of 30	19	14

For the sake of keeping the symptomatology more uniform, we have divided our cases of intestinal endometriosis into two main groups. The first group consists of those having endometriosis involving the rectum, the second consists of those having the lesion higher up in the intestinal tract. There are 41 cases in the group involving the rectum. Twenty have the endometriosis within the layers of the rectal wall, while the remaining twenty-one have lesions adjacent to the rectum with adhesions involving the serosa. The location of the twenty-one lesions is as follows: rectovaginal septum, 6; cul-de-sac of Douglas, 7; sacrouterine ligament, 7; and left broad ligament, 1. There are twelve cases with endometriosis higher up in the intestinal tract with the following organs involved: sigmoid, 6; cecum, 3; ileum, 1; appendix, 2.

TABLE V. SYMPTOMS OF 41 CASES WITH RECTAL LESIONS

Lower abdominal pain	34
Rectal pain or pain with bowel movement	26
Dyspareunia	14
Backache	13
Constipation	9
Pain radiating down thigh	8
Menorrhagia	8
Diarrhea	6
Nausea or vomiting	5
Pelvic pressure	3
Fainting spells	3
Gas and generalized distress	3
Blood in stools	2

The admission complaints of the patients having rectal lesions are listed in Table V. Some patients had several complaints, so the total number of complaints is larger than the number of patients. The complaints in every case were exaggerated just preceding or during the first part of the menstrual period. The longer the duration of the condition, the longer the symptoms continue after each period. In some cases of long standing, the patient finally arrives at the

point where abdominal pain is constant throughout the month. If, however, a history of the onset of the condition is obtained, the symptoms will be confined to the menstrual time. In our series, the length of time the patient waited before coming for treatment or before being diagnosed was three months to ten years. There is a marked variation in how rapidly the pain becomes progressively worse.

TABLE VI. SYMPTOMS OF 12 CASES WITH LESIONS PROXIMAL TO RECTUM

Lower abdominal pain	12
Nausea and vomiting	6
Rectal pain	5
Constipation	5
Gas and generalized distress	5
Menorrhagia	4
Epigastric pain	3
Acute obstruction	3
Backache	2
Pelvic pressure	1

The admission complaints of the group with intestinal endometriosis proximal to the rectum are listed in Table VI. Here, as in the other group, the symptoms are more pronounced during menstrual time. Those developing symptoms of acute bowel obstruction suffer exacerbations at menstruation. The lesion may obstruct the lumen of the bowel, causing it to be reduced to a minute size. In this group, there were three cases with acute obstruction. Two were operated upon by the general surgical service with the mistaken diagnosis of carcinoma and a loop of bowel resected. The third case was diagnosed preoperatively as endometriosis by combined roentgen and pelvic examination. Surgical castration was done, since the bowel was not totally obstructed. This patient rapidly regained normal gastrointestinal function and has gained fourteen pounds in weight.

Our discussion thus far has dealt with the symptoms of intestinal endometriosis, the cases being divided into those of the rectum and those proximal to the rectum. The lesions should again be divided into two separate groups in regard to the histologic findings and also with respect to how these histologic findings influence the clinical symptoms.

Pathologically, intestinal endometriosis may be of the superficial type or it may be of the deep type. The superficial type is by far the most common, and is also the least dangerous clinically. On gross examination, there is a dark puckered area seen grossly on the serosa. On palpation it is a hard nodule varying in size from a buckshot to a bean. Histologically, one finds an island of tissue with endometrial-like glands surrounded by endometrial-like stroma within the layers of the serosa itself. The deep type appears grossly similar but it is larger in size; together with its adhesions it may form very large masses. It is hard and indurated on palpation. Histologically, the deep type is seen as the same endometrial islands as the superficial type, but it is confined largely to the muscular layer of the bowel. In some cases, the serosa and mucosa are entirely intact and the muscularis alone is involved. The Behrendt-Neumeyer case⁴ is an excellent example of both superficial and deep intestinal endometriosis.

This case came to autopsy, and one obstructive lesion with the endometriosis confined to the muscularis and many superficial lesions confined to the serosa were found. Clinically, the symptoms of the superficial lesions is pain, etc., without obstruction. The deep lesions, on the other hand, are likely to sooner or later cause a frank obstructive picture. A number of cases⁵⁻¹⁸ of deep intestinal endometriosis have been reported in the literature, and many of them have the lesion only in the muscularis. A brief clinical history, operative procedure, and pathologic report of two cases of intestinal endometriosis operated upon by the general surgical service and included in this report are as follows:

CASE 1.—A. G., aged 49 years, gravida i, para i. The patient complained of pain in the right lower quadrant for two months, increasing constipation for six months, menorrhagia and dysmenorrhea for two years, and a loss of fifty pounds in one year by diet, from 200 to 150 pounds.

The physical examination was essentially negative. The pelvic examination revealed a uterus enlarged to twice the normal size, moderately fixed, and tender on motion. Roentgenograph showed a filling defect in the upper sigmoid suggesting a neoplasm. A laparotomy was done, and a tumor of the sigmoid found tightly adherent to the uterus, left tube, and ovary. The entire mass was removed, delivering uterus, left tube, and ovary, and resecting a portion of the sigmoid. The liver was normal and no enlarged lymph nodes were found.

Histologic examination: The section of the sigmoid showed the serosa not present due to adhesions. There were islands of endometrial-like tissue throughout the muscular layer and one island in the submucosa. The mucosa was intact.

The patient made an uneventful recovery and later a successful closure of the colostomy was done.

CASE 2.—F. R., aged 33 years, gravida i, para i, complained of pain in the left lower quadrant for one year, severe at last two periods, dysmenorrhea for one year, pelvic pressure relieved by bowel movement for two months, gas and belching for one week. She had had an appendectomy and resection of cysts on both ovaries five years previously.

On physical examination, fullness in the left lower quadrant and acute tenderness were found. The preoperative diagnosis was ovarian cyst. At laparotomy there were found: a cyst of the left ovary 9 cm. in diameter, and a hard constricting tumor on the sigmoid 3 cm. in diameter, having a puckered surface. A biopsy of the sigmoid was done and the tissue found to be cartilage hard. The frozen section was questionable so a Mikulicz type of resection was done. The patient made a good recovery.

Histologic examination: The section of the sigmoid showed the mucosa intact. There were islands of endometrial-like glands, surrounded by endometrial stroma in the muscularis, submucosa, and subserosa.

The diagnosis of the ovarian tissue was a typical chocolate cyst.

In reviewing the histologic sections described in the literature and the cases in our own hospital, one would feel inclined to believe that both of the common theories¹⁹⁻²² of the origin of endometriosis are necessary to prove all cases. Sampson's theory of retrograde menstrual flow through the tube causing peritoneal implants would account for the superficial lesions where the serosa is intact. The other theory of abnormal differentiation of ectopic epithelium would more easily account for the deep lesions. All the organs, in which endometrioses have been found, developed originally from the ectopic epithelium.

The endometrial lesions that cause obstructive symptoms will present characteristic roentgenologic pictures as reported by Jenkinson and Brown.²³ These are relatively long filling defects of four to seven inches, a sharp demarcation

of the filling defects, with other portions of the bowel showing little evidence of disease, an intact mucosa, and exquisite tenderness on palpation during fluoroscopic examination. Proctoscopic examination should be a regular part of this examination to help in the differential diagnosis of the malignant lesions of the bowel.

In carcinoma, the mucosa of the bowel is usually involved, the filling defect is short with sharp irregular margins. The constant filling defect is not usually as tender to palpation as is that of endometriosis.

The fundamental principles underlying the treatment of endometriosis are still undergoing a slow evolution from that of the previous radical procedure of routine castration to one of more conservative individualization. This evolution has come about largely through the efforts of men trained in the art of obstetrics as well as the practice of surgery. This group has led the way in efforts to retain or increase fertility as well as maintain function. Since endometriosis is a disease of the childbearing period and almost one-half of all cases of endometriosis are sterile or relatively so, conservative treatment is more desirable than in almost any other surgical condition. Further, evaluation of the fact that complete removal of all lesions or structures unnecessary for symptomatic or functional cure may lead to a still more conservative attitude in the future.

Several considerations have entered into our choice of procedure and methods of approach in the treatment of this series of patients. First is the extent and location of the lesions. Widespread lesions involving only superficial or relatively unimportant structures we have surgically removed or destroyed with the nasal loop cautery. Deep lesions, such as chocolate cysts and adenomyomas, have been resected in almost direct proportion to the patient's age and parity. Cauterization of the surface of deep lesions, when complete removal seemed too hazardous, frequently gave symptomatic relief. More extensive resection or removal has been carried out irrespective of the appearance of the lesion on the side of the pelvis in which the major part of the symptoms have occurred.

As far as we can ascertain, no one has satisfactorily explained the mechanism of pain in endometriosis. Minute lesions often cause the patient debilitating pain, while widespread involvement may occasion only slight discomfort. We have reserved x-ray castration for those patients in whom a surgical attempt has been made to correct the condition and in whom the histologic diagnosis leaves no doubt as to the benign nature of the lesion.

The vaginal approach, both as a diagnostic procedure as well as an avenue of treatment, has found increasing favor on our service. Many cases with small endometrial lesions have been operated upon at the proper time through the diagnostic use of posterior colpotomy rather than waiting until gross destructive lesions have appeared. One has much less hesitancy in advising a surgical procedure which is so safe and relatively painless as is colpotomy, to say nothing of the shorter convalescence required as compared with the simplest laparotomy. Small lesions lying at the bottom of the cul-de-sac or in the sacro-uterine liga-

ments, or even in the ovaries, may be treated per vaginam as accurately as through the abdominal incision. If hysterectomy is indicated and especially if repair of the perineal floor is also necessary, even more extensive endometrial lesions may be adequately cared for through the ordinary vaginal hysterectomy incision. In fact, some lesions, such as low-lying adenomas of the rectovaginal septum or ovaries fixed low in the cul-de-sac can be reached by vaginal approach more readily than through an abdominal incision.

If at any time during a vaginal operation removal or exposure of lesions becomes impossible, closure of the vaginal vault followed by abdominal incision will not appreciably increase the morbidity to the patient. Most gynecologic clinics do not hesitate to do ordinary vaginal repair followed by intraabdominal pelvic procedures. We do not feel, however, that the vaginal approach should ordinarily be chosen under the following conditions:

- a. In patients whose clinical symptoms suggest involvement of the bowel.
- b. For those patients in whom sterility is of first importance.
- c. Grossly extensive lesions associated with fixation of organs.
- d. In instances of fixed retroversion which cannot be easily reposed.
- e. Where extraneous symptoms may indicate of themselves abdominal exploration.

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ASPHYXIA OF THE NEWBORN INFANT

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IN ORDER to contribute to reduction of the considerable death rate in the newborn infant, continued emphasis must be placed upon prophylaxis and treatment of cyanosis or apnea. In recent years a number of studies have been made upon the cause of this apnea. In 1941, we published a preliminary article¹ on our experiences in the resuscitation of the newborn infant, based upon 196 cases. Since then, 1,048 additional resuscitations have been effected and have made the following observations possible.

Asphyxia, or the better term, apnea, is defined as an interference with the oxygenation of the blood stream, or, clinically, it may be expressed as the lack of spontaneous effort to take a breath within thirty seconds after the cord is severed. After this period of time, definite cerebral changes will take place from anoxemia, and if oxygenation of the blood stream does not occur within one or two minutes, there will be definite permanent cerebral changes. Oxygenation before this time will overcome any changes which will have taken place.

Causes of Asphyxia

Most frequently the causes of asphyxia are found in the mother and in the handling of the mother during labor. These causes may be classified into two large general categories; those which occur before labor, and those which occur at the time of labor and delivery. In general, the prelabor group plays little or no part in producing asphyxia of any severe nature. However, it may be the precipitating factor added to any other cause, which may result in a severe asphyxia. In the category of causes occurring before the time of labor and delivery may be included such factors as:

Age of the Mother.—It is definitely known that an arbitrary line may be drawn at the age of 35. After 35, mothers are more likely to deliver an asphyxiated baby than they are prior to this age.

Parity of the Mother.—In general, primipara produce more asphyxiated babies than do multipara. This can be generally explained on the basis that more cerebral trauma is likely to occur in the baby of a primiparous mother than among those of multiparous mothers. However, in the multiparous mother, for some undetermined reason, the third, sixth, eighth, and eleventh babies seem to have a greater tendency toward asphyxia than do the others.

Profound anemia in the mother should be especially emphasized as, in practically all cases, any mother who has an anemia of less than 3,000,000 red cells, will usually give birth to a baby with less than 4,500,000 red cells, which in two or three days is quickly reduced to a level below 3,000,000. With this reduction of oxygen carrying power, naturally, cyanosis is quite liable to occur.

TABLE I. DISEASE CONDITIONS OF THE MOTHER

-	Cardiac disease
	Kidney disease
	Profound anemia
	Diabetes mellitus
	Tuberculosis
	Syphilis

Causes at Time of Labor

The most important and numerous group at the time of labor and delivery must be considered in more detail. In most cases, two or three causes exist at the same time, and the combination produces severe or moderate asphyxia.

Duration of Labor.—It is becoming increasingly evident that the prolongation of labor is by far the most outstanding single cause of asphyxia of the newborn. It has been too easy to blame the analgesic drugs, but the asphyxia the drugs produce is by no means either as frequent or as severe as that produced by a prolonged labor.

In primiparous mothers, when the first stage of labor has been twelve hours, or the second stage of labor has been six hours, the incidence of asphyxia rises sharply. When the first stage of labor has passed sixteen hours, or a second stage of labor has passed eight to nine hours, over 80 to 85 per cent of all babies may be expected to be born asphyxiated. In the multiparous mother, the same is true, but the length of labor which may be endured without asphyxia in the first stage is only eight hours, and in the second stage only four hours. This seems paradoxical, for the multiparous mother should not be producing as much obstacle to the delivery of the baby as is expected when she delivered her first. However, in the multiparous mother, who has had relaxation of bone and ligaments, if delivery is prolonged, the effort to push the baby through the birth canal is so much greater than is normally expected that cerebral trauma ensues.

TABLE II. TYPE OF DELIVERY

TYPE OF DELIVERY	ASPHYXIA RATE	DEATH RATE
Version & extraction	80-90%	25-35%
High forceps	80-90%	25-30%
Breech extraction	60-65%	12-15%
Midforceps	50-60%	10-12%
Cesarean sections	85-95%	8-10%
Low forceps	15-25%	3-5%
Spontaneous delivery	10-20%	2-3%
Low forceps with episiotomy	10-20%	1-3%

The above figures point out many interesting facts. They definitely show that the more traumatic the type of delivery, the higher the death rate and asphyxia rate. The amount of analgesia necessary during labor, and the depth and type of anesthesia necessary, all contribute to produce asphyxia; consequently the type of delivery is not the sole cause. However, in many cases, the type of delivery will produce a cerebral hemorrhage to the extent that asphyxia will occur.

It is interesting to note the asphyxia and death rates in cesarean sections. In many cases, physicians have proceeded to do a cesarean section with the belief that they were protecting the baby by giving it a better chance for life. This is far from being the truth. In a previous study at Touro Infirmary in New Orleans, it was found that the average death rate in cesarean sections, when no intratracheal catheterization had been done, ranged from 9 to 10 per cent. The average death rate, when intratracheal catheterization was performed, was lowered to less than 2 per cent. Studies on those babies who died without having had proper resuscitation revealed some very interesting details. They lived on an average of 17 to 21 hours, with ranges of from 4 to 47 hours. Their clinical course was quite strikingly the same. In most cases they breathed spontaneously, or after a few minutes breathed without a great deal of stimulation. They remained pink and breathed rhythmically for a period of two to three hours, after which time they turned suddenly cyanotic. Each was revived with a little difficulty, and usually placed under oxygen, whereupon the baby remained pink and breathed easily for a period of another few hours. Suddenly it turned cyanotic again and was revived with even more difficulty than previously. This time under oxygen it did not breathe rhythmically. After several more hours, the baby turned very definitely cyanotic and with a slate gray appearance remained so, breathing with more difficulty. The respiration would then become more shallow until death occurred on an average of about 18 hours after birth. Pathologic examination of these lungs revealed that those alveoli which had been opened were lined with pseudo membranes consisting of amniotic fluid, meconium, lanugo, blood, and other detritus commonly found in the upper respiratory passages of a newborn baby. This, therefore, may be termed a pneumonia due to the aspiration of amniotic fluid. It has been too frequently termed congenital atelectasis of the newborn. It is not an atelectasis. It is truly an aspiration pneumonia.

It has been commonly known that the average baby born from cesarean section does not breathe as spontaneously or as quickly as a baby delivered by other methods. Reasons for this have never been definitely determined. The squeezing action on the lungs and head produced by the passage through the normal birth channel is probably the major stimulus for the baby to breathe. However, this does not seem to be the full truth. In our experience, the average cesarean section baby will not breathe spontaneously within the conventional time limit of thirty seconds previously mentioned. In such cases, it is extremely necessary that a routine intratracheal catheterization be done. When catheterization is performed, 3 to 7 c.c. of thick mucoid material is aspirated. In many cases, much more is frequently obtained from the trachea. In the average newborn delivered through the normal birth channel, aspiration of the tracheal passage usually yields about 1 or 2 c.c. of the same material. In comparing again the results obtained with routine intratracheal catheterization, as compared to no intratracheal catheterization, the death rate is strikingly different. In the former, out of 317 cases performed routinely, only six deaths occurred. This is a death rate of 1.8 per cent. During the same time,

137 cesarean sections with no subsequent intratracheal catheterization of the baby were observed with twelve deaths, a death rate of 8.7 per cent. This is too striking a coincidence to be disregarded. Here it is noted that of the six deaths, which occurred after routine intratracheal catheterization, five were autopsied and found to have massive cerebral hemorrhage. In the twelve deaths of those who did not have routine intratracheal catheterization, eleven were autopsied. The one which was not autopsied was found to be congenital atelectasis of the newborn and had a strikingly similar course to that described previously. Of the other eleven deaths, two died from cerebral hemorrhage, and nine died from aspiration pneumonia, previously described, having been regarded as either asphyxia neonatorum or congenital atelectasis of the newborn. In other words, ten out of twelve died, when probably these deaths were preventable. It is our very firm and definite conviction that, if a routine catheterization of the newborn be done at every cesarean section immediately upon delivery, the death rate can be reduced from an average of from 8 to 10 per cent to as low as 2 per cent.

Prepartal Analgesia.—In our previous paper, we presented a rather detailed discussion of most of the drugs used in obstetrics. We can add little or nothing to change any of the statements made at that time. Our observations on the use of morphine have been confirmed. A definite narcosis was noted within four hours. Morphine, therefore, should never be given where delivery is expected within four hours. Scopolamine has a definite cumulative depressing effect, if more than $\frac{1}{50}$ grain is given within a period of twenty-four hours. In general, the barbiturates have little or no effect on the baby unless such an amount is given to cause a depression in the mother. However, there is one notable exception to this, and that is the use of nembutal (pentobarbital sodium), which causes a very severe and profound asphyxia of the baby.

In our previous paper, attention was called to the fact that as little as $1\frac{1}{2}$ grains (0.09 Gm.) four to six hours prior to delivery has produced narcosis in the child. The effects of pentobarbital sodium begin to appear in the infant about thirty to forty-five minutes after the drug is taken by the mother, and they are long lasting, still being present six to eight hours after ingestion; the effects reach their height about two hours after ingestion and remain at a maximum for the next two hours. The infant born under the effects of pentobarbital sodium presents such a characteristic appearance that an observer familiar with the appearance may realize merely by looking at the baby that pentobarbital sodium has been given to the mother. The baby is a deep purple, limp, with absolutely no reflexes; he breathes with difficulty only after from ten to thirty minutes of intensive resuscitative efforts and then fails to maintain respiration well, repeated resuscitations being necessary before a regular rate of respiratory rhythm is established. The baby has several cyanotic attacks and cessations of respiration during the first twelve hours of life and needs close and careful attention, fails to cry at all for the first eight to twelve hours of life and is indifferent to all sorts of stimuli for twenty-four hours after birth. Even after respiration is well established, the purple color lingers

on the hands and feet for from twelve to twenty-four hours; the heart rate is rapid and the pulse is shallow; circulation appears to be poorly established.

The foregoing observations seem fully to justify the assertion that the use of pentobarbital sodium should be discontinued and that morphine should not be administered if delivery is possible within four hours. Greater reliance should be placed on the relatively harmless barbiturates.

Newer drugs since our previous paper include demerol, and we have been able to observe in the past year approximately 100 or 120 cases in which it was used. Little or no effect is noted on the baby when delivered. The use of caudal analgesia has been watched closely, and as is the experience of many others, no effect is noted on the baby to any great extent, that can be attributed to the effect of the drug.

Anesthesias.—Chloroform: This drug is not widely used in the United States, and has a severe depressing effect on the baby when used and, as its margin of safety is so small, it should be administered only by an experienced anesthetist.

Ether: This is probably the most widely used anesthetic in the United States, and has little or no effect on the baby that cannot be overcome rather easily.

Cyclopropane: Cyclopropane evidently should be given only by a very experienced anesthetist, as it seems to cause more trouble than any other gas anesthetic. Not only does it produce some asphyxia, but it seems to produce a secondary shock to the baby about four to six hours after it is delivered. We have noticed that babies delivered under cyclopropane anesthesia, some four or six hours later, have a little perspiration and their temperature is generally one to one and a half degrees lower than the average newborn, coexistent with a tendency to vomit, and suckle less than the average baby.

Ethylene: Ethylene seems to produce no effect on the baby of any great note.

Intravenous anesthetics are mentioned to be severely condemned for use in obstetrics. The death rate for both the mother and the baby is too high to consider their use in pregnancy.

Spinal Anesthesia: The added danger of sudden drop in blood pressure of the mother is a deterrent to the use of this particular technique.

Miscellaneous Causes.—Other factors may cause cyanosis of the newborn. Included among these are prematurity; premature separation of the placenta; bleeding placenta previa; short cord or prolapse; knot, kink, or compression of the cord in the mother. Prematurity is in itself such a notable cause of asphyxia that it must be especially mentioned. However, its prevention is a matter to be considered with that of preventing the delivery itself, and not that of preventing asphyxia.

The foregoing are, in general, the major causes of asphyxia in the newborn. The recognition of them suggests the proper prophylaxis. Further emphasis must be placed on the fact that usually more than one cause exists to initiate asphyxia in a newborn. No single factor, except cerebral hemorrhage, usually produces a severe asphyxia in a newborn.

Methods of Resuscitation

Asphyxia has been classified for a long time under two types: asphyxia pallida and asphyxia livida. These two are vague terms and mean nothing, as the average baby who is delivered severely asphyxiated may be of either color. A much better classification is that suggested by Flagg,² which is as follows:

Mild Asphyxia.—The infant resists movement of the head and limbs. Mucous plugs and amniotic fluid fill the mouth and pharynx. Muscle tone is good, conjunctival reflexes are present.

Moderate Asphyxia.—Muscle tone is absent. There is no resistance to opening the mouth. No reflex irritation is induced by aspiration or by stimulation of the glottis.

Severe Asphyxia.—The infant does not respond to attempts of resuscitation. He appears livid or pallid. There is absence of any respiratory movement, and only an occasional flicker of the cardiac impulse may be detected through the thoracic wall. The upper respiratory tract has become a collapsed tube. All reflexes are naturally absent.

The outstanding factors in this particular condition are the absolute listlessness of the baby; the very slow heart beat; and the definite appearance of a dead baby.

Principles of Resuscitation

In order to have any good resuscitation, four major principles must be followed. Each of the following principles is of equal importance and no technique of resuscitation can lack any one of them and still be a good method of resuscitation. These are:

1. A minimum of handling.
2. Immediate warmth.
3. A clear open airway.
4. Oxygenation of the blood stream within 30 seconds of severing the cord.

The first thing necessary in resuscitating a baby is to avoid severing the cord until it has ceased to pulsate. Cutting the cord as soon as possible deprives the baby of 80 to 200 c.c. of very necessary blood, and if it has a tendency to asphyxia, it is consequently deprived of from 25 to 30 per cent of its oxygen carrying power. As soon as the cord has been severed, the baby should be received into something warm and put down upon a flat surface immediately. With the use of an intratracheal catheter, the nose is first aspirated. This is a very powerful reflex toward the stimulation of respiration and in the case of mild asphyxia, may alone be sufficient to initiate respiration. However, if the baby has shown no attempt to breathe, the mouth, gums, under the tongue, lips, cheeks, and nasopharynx must be aspirated. If the baby shows no attempt to breathe, the catheter is then gently introduced about one-half inch into the trachea which is aspirated first, and then by means of the resuscitator's own breath through the catheter and bulb, the chest is gently inflated and allowed to deflate by its own elastic recoil, at a rate of from 24 to 30 times per minute. It is only necessary to inflate the chest sufficiently

to cause the chest wall to start to expand. Further inflation may cause damage. Deflation is not necessary, as the elastic recoil of the lung will provide its own expiration. After this has been done for a short time, and if oxygen is available, the baby may be given pure oxygen by means of one of the better resuscitators, if it is on hand at a hospital.

Probably the best resuscitators available today are the Ericson and Johnson and the Henderson machines. These provide definite pressures of oxygen. In the case of the E. & J., there is mechanical deflation, while in the Henderson machine, there is no deflation, the elastic recoil of the lung doing its own work. However, if no machine is available, it is only necessary to continue inflation of the lung by means of the resuscitator's own breath. This is frequently as effective as any machine. As soon as the baby has taken a few breaths, and has started even a short rhythm of respiration, it is given 100 per cent oxygen, preferably. This may cause a slowing up of respiration, but will result in deeper breaths, and inflation of the lungs to a greater extent producing a better rhythm of respiration. The use of 5 per cent carbon dioxide and 95 per cent oxygen is very good, but it seems to cause, in many cases, a cessation of the rhythm which has been previously established. The use of stimulating drugs such as alpha-lobeline, coramine, metrazol, caffeine-sodiobenzoate, adrenalin, seem to have little or no beneficial effect. After respiration has been established, the use of coramine in dosages of four to six minims may help the heart rate, and possibly aid the rhythm of respiration. However, this is doubtful, and any reliance on stimulating drugs is depending on a broken reed. Alpha-lobeline is strongly advocated as an excellent method of resuscitation. Our experience is that drugs have no value—actual aspiration and subsequent insufflation of the lungs is the truly reviving technique.

Aftercare

The aftercare of the newborn resuscitated baby is of equal importance to that of the resuscitation itself. Too frequently this is overlooked. Such a baby must be treated as if he were very sick, and as if he were a premature baby. The following instructions should be followed:

1. The baby should be placed in an incubator at approximately 90° F.
2. Oxygen should be given continuously for at least six to twelve hours.
3. Careful observation of the baby must be made every fifteen or twenty minutes, if he has no special nurse.
4. No feeding is offered for the first twelve to eighteen hours.
5. Coramine (dosage minims 4 to 6) may be given at thirty-minute intervals, if the heart beat seems to be too slow, or if the respiration seems to be flagging.
6. Carbon dioxide, 5 per cent and oxygen, 95 per cent should be given as inhalation for one to two minutes every thirty minutes for the first six hours to aid in deeper respiration and to inflate more alveoli.

The above aftercare is much more important in those babies which have been severely and moderately asphyxiated than in the milder cases. Every case must be individualized, and the above orders must be changed as circumstances warrant.

The results obtained by the application of the principles which we have found to be effective in the recognition and relief of asphyxia in 1,048 additional newborn infants to the 196 previously reported have been analyzed, and our observations are tabulated as follows:

TABLE III. RESULTS OF RESUSCITATION

TYPES OF ASPHYXIA	NO. OF CASES
(a) Mild	471
(b) Moderate	420
(c) Severe	157
	1,048

TABLE IV. LENGTH OF TIME NECESSARY TO INITIATE RESPIRATION

Less than 5 minutes	812
5-10 minutes	139
10-15 minutes	36
15-30 minutes	27
30-60 minutes	17
1-2 hours	10
2-3 hours	2
3-4 hours	4
4-5 hours	1

TABLE V. RESULTS OF RESUSCITATION

Unable to start respiration	1
Respiration maintained less than 1 hour	4
Respiration maintained longer than 1 hour but less than 4 hours	15
Respiration maintained longer than 4 hours but less than 24 hours	49
Respiration maintained longer than 24 hours	979

TABLE VI. DEATHS

Infants with mild asphyxia	3
Infants with moderate asphyxia	14
Infants with severe asphyxia	52

TABLE VII. CAUSES OF DEATH

Prematurity	29
Intracranial hemorrhage	29
Malformation	4
Erythroblastosis foetalis	2
True congenital atelectasis of newborn (pneumonia alba)	3

Discussion

Anoxemia, from many causes, is responsible for 18.5 per cent of all deaths in newborn babies. It is fourth in the causes of death in this age group. Among the most frequent contributing factors of anoxemia are the age and parity of the mother, duration of labor, type of delivery, prepartal analgesia, and the anesthetics used during delivery. Less frequently, prematurity, premature separation of the placenta, bleeding placenta previa, short cord, pro-

lapse, torsion, knot, kink, or compression of the cord may cause it. Anoxemia prolonged more than two minutes after delivery will cause serious cerebral changes. But the prompt initiation and maintenance of respiration within thirty seconds after cutting the cord will prevent these changes, and if it is established before two minutes it may oxygenate the blood sufficiently to arrest any changes which have begun.

Consequently, it is absolutely necessary for anyone accepting the obligation of caring for the newborn, whether he be the obstetrician, pediatrician or general practitioner, to familiarize himself with the causes and treatment of asphyxia in the newborn, if any reduction is to be made in this preventable cause of death, which contributes so largely to the death rate of newborn babies. The death rate among the newborn has not been reduced in the same proportion as it has been in other age groups in early life during the past forty-five years. Continued study and close observation will enhance our knowledge so that we shall more effectively lower the percentage of this cause of death in newborn babies.

Conclusions

The results of the study of 1,048 additional cases of asphyxia to the 196 previously reported are analyzed and tabulated.

The prenatal and natal predisposing causes of asphyxia, the means of preventing them, and the basic principles and methods of resuscitation are discussed.

More general appreciation and recognition that it is necessary to be alert to any delay in the spontaneous initiation of respiration in all newborn babies immediately after birth is suggested as an urgently indicated preventive measure to reduce the high death rate from anoxemia.

The acquisition of the knowledge necessary to safeguard all newborn babies from asphyxia and treat them if it occurs, is an obligation which must be assumed by everyone who accepts the responsibility for the care of the newborn.

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PRECONCEPTIONAL PROGESTIN THERAPY IN HABITUAL ABORTION

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MANY of us concerned with the problems of sterility are given credit for therapeutic triumphs which are not rightly ours. According to our present concepts and contrary to lay opinion, any young vigorous female who has been impregnated by an equally young vigorous male faces a fairly considerable chance of spontaneous abortion of a "bad egg," the pathologic ovum which Nature usually suspects, inspects, and discards in the first trimester of pregnancy. Should this patient then consult a "sterility expert," and should she go through a subsequent pregnancy normally under his guidance, credit usually goes to the doctor rather than to the patient's statistical chance of maintaining instead of discarding the fertilized ovum.

The acid test of any therapeutic plan for improving the statistics of lost ova lies in the treatment of the so-called "chronic or habitual aborters."

The subprimate mammals show a 30 per cent ova loss, as determined by the discrepancy between the number of corpora lutea and the number of embryos in the litter. These investigations in the sow and opossum indicated that of the ova ovulated, three in ten either defied fertilization or, if fertilized, soon ceased to develop and were then absorbed with no recognizable evidence of pregnancy remaining therefrom. Figures in human fertility have been difficult to come by.

Mall²² found that 48 per cent of his entire collection of abortions were pathologic. Hertig¹³ found 46 per cent of his series were pathologic, accepting as a "pathologic ovum" one which could be demonstrated either grossly or microscopically to be deficient in development. These ova cannot be separated into true primary germ plasm defects or into ova which, though inherently good, undergo an aberration of development due to defective secundines, inadequate circulation, poor implantation, and to local or general causes. The final common denominator is the "pathologic ovum" which is a recognizable entity.

Mall²² and Streeter²⁸ found that only one-fifth of the embryos aborted at the end of the first month were normal, whereas of those aborted in the close of the second month one-half were normal. In the third and fourth months, eight-ninths of the aborted fetuses showed no evidence of pathologic changes. In the latter half of pregnancy, abortions due to pathologic ova no longer are found. These premature labors are explainable on the basis of mechanical fault of the supporting structures, such as faulty implantation, faulty placentation, inadequate maternal circulation or abnormal uterine irritability. Monsters surviving to term represent anomalies too slight to cause spontaneous termination of pregnancy.

Pathogenesis of the Pathologic Ovum

Factors in the pathogenesis of the pathologic ovum are still controversial. A positive statistical correlation has been found between the occurrence of certain states and the occurrence of spontaneous abortion.

1. Defective germ plasm, the true "pathological ovum."
2. Nutritional states, such as avitaminosis, lack of food factors, and poisons.
3. Abnormalities of the generative tract, such as fibroids, infections, retroversions, and lacerations.
4. Incretory disturbances, such as disturbances of hormone production (pituitary, thyroid, ovary, adrenal, etc.) which manifest themselves in defective decidual reaction, genital hypoplasia, and adiposity.
5. Chronic system disease, such as syphilis, nephritis, toxemia, focal infection, undulant fever, endometritis, anemia, chronic passive congestion, and infarcts.
6. Trauma and fatigue.

It is extremely difficult to discuss the factor of defective germ plasm. If we accept the "inevitable human wastage" as about 10 to 20 per cent of all fertilized ova, then our concept is modified greatly. Malpas²³ studied 6,000 pregnancies, finding a spontaneous abortion rate of 18 per cent. Interpreting these pregnancies on a chance-variation basis, he reached the conclusion that chance factors were not ruled out until three successive abortions or stillbirths had occurred. In other words, recurrent factors could not be said to be in operation (so that abortion could be regarded as "habitual") until there had been three consecutive failures. With this in mind, one is loath to call the patient's hereditary constitution "defective" quite as readily as before. We can easily study the morphology of the male germ cells, and investigations show that an incidence of abnormal forms up to 20 per cent may be no hindrance to satisfactory reproduction. A higher incidence is associated statistically with an increased number of abortions. The female germ cells and their early fertilizations are extremely difficult to study, and therefore we have no comparable data in the female. Present work on the recovery of unfertilized ova from the abdominal cavity, the tubes, and the uterine cavity may give us additional information, and much has been learned of early embryonic life through the work of Streeter, Hertig, Rock, and others. Suffice it to say, that there is nothing specific at the moment which we can do about preventing defective germ plasm save general hygienic measures.

Accordingly, we may describe "defective germ plasm" as an intrinsic weakness in the cell, apart from any other factors which could affect it, rendering it unfit to carry out the normal succession of developmental events and causing the appearance of structural and functional defects. An important school of thought suggests that physical and environmental factors are more effective than is yet realized, that endocrine factors may be able to alter the physicochemical anatomy of the fertilized ova so as to produce ultimately pathologic ova. Ninety-six per cent of 46 tubal gestations studied by Mall²² were abnormal, which is a much higher figure than can be accounted for in ordinary population samples. This suggests that the abnormal environment has played a part in the abnormal development of the ova. In lower forms of life as well, many anomalies such as spina bifida, anencephalus, and the like, can be produced artificially by stimulating eggs with various substances, for instance, by hypertonic salt solution, weak galvanic currents, or mechanical irritation.

Malpas.²³ in his interesting statistical study of 6,000 abortions, found that if the patient has had but one abortion previously, she has a 78 per cent

chance of not repeating it. If she has had two abortions consecutively, she has a 62 per cent chance of not repeating. If the patient had had three previous consecutive abortions, only 27 per cent of untreated patients will carry to term; and with four previous consecutive abortions, only 6 per cent would not repeat. *It is not until the patient has had three consecutive spontaneous abortions that random and chance factors can be excluded.* These, then, are the "chronic or habitual aborters" who constitute a formidable group for study in sterility techniques.

Physiology of Progestin

There is ample evidence that the glands of internal secretion are either directly or indirectly concerned with the inception and maintenance of pregnancy. Disturbances of such relationships may affect the continuance of pregnancy. It is suggested that in the human being the successful continuance of gestation depends in part upon the normal balance between estrogens and progestin. Present evidence indicates that before and during the attachment phase, these hormones are supplied by the ovary and later by the placenta as chief supply.

Several critical points must be passed before a pregnancy can be viewed in salubrious fashion. Should the patient have had persistent follicular activity with a consequent excess of estrogen prior to conception, the usual hyperplastic endometrium is a doubtful bed for nidation due to its glycogen-poor, infarcted, unsatisfactory pregravid state. Even though nidation should take place, its tenure may be short because of surrounding endometrial hemorrhages. The finding of excess estrogen in the body fluids in cases of inevitable abortion would suggest that the uterus might be refractory to the influence of the corpus luteum of pregnancy. Shute²⁶ feels that such an excess may leave the endometrium relatively impervious to the invasion tactics of the fetal trophoblast. Cases of uterine hypoplasia due to inadequate pituitary gonadotrophic and/or estrogen stimulation are obvious. However, repeated abortions with their endocrine barrage have been known to develop the genitals more effectively than the clinician's ampule.

The gonadotropins, as well as the estrogens, have been the subject of many studies, but none conclusively point the way for clinical attack. On the other hand, observations⁸ in the animal point more conclusively to the role of progestin in early pregnancy, the so-called critical period for the habitual aborter. A progestin deficiency arising prior to implantation may be responsible for inadequate preparation of the endometrium. In the event of conception, the fertilized ovum finds the nidation bed unsuitable, and early death and resorption follow. In the rabbit, the fertilized ovum will not implant if the corpus luteum is removed shortly after fertilization has taken place. This can be prevented by the administration of progestin.⁸ Where the deficiency arises after implantation takes place, the resulting impairments in myometrial blood supply, poor glandular secretion, and uninhabited motility of the uterus may cause either resorption or abortion depending upon the stage of pregnancy.

Browne, Henry and Venning,⁵ on the basis of pregnandiol excretion in normal pregnancy and spontaneous abortion stress progestin deficiency as a cause

of abortion. This failure was prone to appear at the time of the transfer of progesterin secretion from the degenerating corpus luteum of pregnancy to the placenta. This may be due to premature regression of the ovarian corpus luteum³ or to late assumption of its role by the placenta. This should take place sometime between the tenth and fourteenth week. In certain cases it is found¹² that the corpus luteum will undergo premature degeneration in either the nonpregnant or pregnant state. The former has been indicated by specimens of supposedly progestational endometrium which have shown faulty maintenance. The latter has been known to take place even before implantation occurs.

Plan of Study

Some five years ago, the study was started using patients who had had three consecutive sequential abortions. This, according to Malpas' criteria, would eliminate chance or random factors as cause for abortion. In addition, it seemed that one agent and only one agent should be used in this group of patients since too many conflicting therapies would nullify the conclusions. Reports^{9, 10, 11, 18} using thyroid for one or both partners, the vitamins, the gonadotropes, even the estrogens and androgens, have been published. Often a combination of these factors was used, making evaluation of any one agent even more difficult.

It seemed reasonable to attack the problem of repetitive abortion therapy from the standpoint of prevention, rather than to rely upon frantic treatment established after uterine bleeding and/or uterine cramps had established themselves. Since these latter evidences would suggest a pathologic ovum, it again seemed reasonable to plan for the prophylactic phase rather than for the therapeutic phase. In other words, our best opportunity to influence proper nidation is before the patient's first missed period, during the critical few days between fertilization of the ovum and implantation. Since progesterin seems implicated more definitely than any of the other available hormones in development of proper progestational endometrium, in promoting adequate vascularity, and in quieting uterine motility, then it seemed that progesterin supplied in large amount from the preconceptional period onward was a logical start.

Abundant laboratory investigation in these cases with bio-assay techniques have yielded results difficult of interpretation. Therefore, a simple, relatively inexpensive way for treatment of the office patient was sought. There were no laboratory studies done on these patients except the occasional test incident to investigating the good health of both partners. Both partners were given a routine of a balanced diet, adequate vitamin intake by diet, and accepted habits of rest, exercise, and the like as far as our present confused civilian life would permit. The husbands were of proved fertility, with sperm counts of 50 million or better, with no more than 20 per cent of abnormal forms. The female patients were shown to ovulate habitually by endometrial biopsy if suspicion of abnormal catamenia was raised. Tubal patency was not investigated unless indicated. Cervical erosion, adnexal or uterine tumors, malpositions of the uterus, all were corrected. They were an average group of clinic and private patients who showed only the wear and tear of repeated pregnancies.

It is difficult to determine the accepted amount of progesterin which the patient should be given. Browne, Henry, and Venning⁵ have found that 10 to 20 mg. of progesterin are excreted daily in normal pregnancy. If this be taken to indicate the amount of progesterin metabolized, it may be that at least 10 mg. must be given daily. Progesterin injected is recovered in the urine within 24 to 36 hours, which would seem to delimit the duration of action of artificially given hormone. Less hormone may be given if the patient misses her period and is presumably pregnant. If the facilities are available, deficient pregnandiol excretion would suggest a possibly deficient corpus luteum.

The patient was taught to calculate her fertile period, beginning some eighteen days before flow was anticipated, and continuing through until the tenth day before flow. She was taught to give herself injections of 5 mg. of progestin every other day beginning the eighteenth day until flow supervened. No disorder of the usual menstrual cycle was encountered, although it is well to caution one's patient that the normal cyclical variation of menstrual flow is from two to five days. Exposure to pregnancy was started on the eighteenth day and continued every other day until the tenth day before flow. This forty-eight-hour respite had been considered necessary for the average male to regenerate an effective charge of sperm. The patient was cautioned to lie quietly on her back for an hour after exposure. No other variation of position, preliminary douche, etc., were recommended. Should the patient miss her flow, she continued her shots every other day until the beginning of the fourth month, and then every third day until fetal motion was felt. From thence onward, it was felt that placental sources had long since superseded artificial sources. The parenteral route was chosen for constancy of dosage and absorption. By the oral route, many times this dosage must be given. No individual sensitivity to the progestin shots developed, although the problems of carrier sensitivity and possible anti-hormone formation were considered.

A preliminary report²⁵ was issued several years ago which listed the results in 23 cases. This is a further elaboration of the series, with a slightly different routine than that originally outlined. A total of 63 cases has been collected. Of these, 54 had had three consecutive abortions, and nine had four or more abortions. The age varied from 19 to 41 years, and all were in good physical condition as far as could be determined. Of the total, eleven had had one or more previous living children, whereas the remainder had never had a living child. Interestingly enough, the incidence of so-called germ plasm defect (or pathologic ova) was much higher than a random population sample would show. In other words, in such a highly selected group of cases, we should expect primary germ plasm defects to run much higher than the usual 10 to 20 per cent. Figures will be given for each group.

Group I was composed of patients who had had three consecutive abortions. Fifty-four of the 63 cases fell into this group. Thirty-one of the 54 went on to deliver viable infants (28 weeks or better) although only 21 went to full term. Of the ten who did not go to full term, three infants died of prematurity and its problems, one of the infants was erythroblastotic with acute hydrops in the mother. In other words, 31 of the 54 delivered viable children, with 28 infants surviving. This would give a percentage of 57.4 or, if we exclude the three cases losing their babies from problems of prematurity, the percentage would correct to 51.8. In Malpas' statistical sequence, this group of cases would expect a fetal survival of 27 per cent.

Of the 23 cases who aborted, the abortion calendar ranged from five weeks menstrual age to 25 weeks. The incidence of proved pathologic ova was 69.1 per cent, whereas the remainder were normal embryos with defective maintenance.

In Group II were nine cases who had had four or more consecutive abortions. Some of the Group I cases moved on to add to the statistics of this group. In this group, only four of the cases carried to viability, with one premature who survived and the other three being full-term infants. Of the five patients in this group who did become pregnant, but did not go to viability, two patients had normal embryos, all other cases having pathologic ova. The salvage rate in this group then was 44.4 per cent. Malpas' figures for an untreated group were an expected salvage of 6 per cent.

In Group III were a number of cases who had had sequential abortions, but who either became discouraged, or who did not become pregnant despite this routine. If the latter were the case, often additional agents were employed or specific treatment was needed, such as correction of tubal occlusion, treatment for achievement of ovulation and the like. These cases have not been noted.

Two case histories are recorded in more detail to illustrate peculiar problems. Case histories of successful outcome we all can duplicate.

CASE 1.—Mrs. W. W., a 31-year-old housewife, had one adopted child. She was seen first in 1942 with a story of three previous spontaneous abortions in the last five years. No examination of the embryo had been done at any time, but, because she had failed to go through more than the first three months, these were presumably pathologic ova. General examination was negative and evaluation of her reproductive system was normal. She had never experienced difficulty in becoming pregnant, nor did she in this, her fourth pregnancy.

She was started on the preconceptional routine, and after one period had no further bleeding. Pregnancy was confirmed, and she went along normally until approximately 17 weeks, when, without warning, she bled and passed what was an entirely normal embryo of that gestational age. The placenta was completely circumvallate, and the point of rupture of the membranes was at the margin of the placenta. This would suggest a shallow-implanted ovum in the lower uterine segment.

Not discouraged, she became pregnant again after a single period. This pregnancy went up to 22 weeks, with fetal motion present, and a fundus which reached to two fingers above the umbilicus. However, she aborted again. The embryo was normal and of proper gestational size, with a placenta which had the identical findings of the previous one.

Progestin was continued all through the last pregnancy in larger amounts than usual, and will be continued in any subsequent effort. Under treatment, she has extended the intrauterine maintenance of the ovum.

CASE 2.—Mrs. L. M., a 29-year-old housewife, had first a premature labor, resulting in the delivery of a female infant weighing over 3 pounds which survived. Her next three pregnancies resulted in spontaneous abortions during the first three months. Her doctor made no report on these embryos. She embarked upon the routine for her fifth pregnancy, and carried through to 31 weeks, when she went into premature labor and delivered a 3-pound 11-ounce female which survived. The placenta was completely circumvallate, but was implanted in the upper uterine segment according to measurement of the point of rupture of the membranes.

This infant, a normal child, died of pneumonia at seven months of age. The patient wished to become pregnant again, and, under the treatment, which had been stopped at fetal motion before, went up to 29 weeks, when she said she had felt no fetal motion for several days. Auscultation failed to reveal any fetal heart tones, but she was watched for another week to be certain. It was felt to be too early for x-ray changes to appear. During this waiting period, the patient went into rapid labor of less than an hour. She delivered a macerated fetus, whose accompanying placenta showed erythroblastotic changes on microscopic examination. The father was Rh positive, as was the infant, a male. The mother was Rh negative. Her previous infant which had survived to seven months had been a female and had not been Rh tested.

Because of the introduction of this serologic problem of Rh positivity and negativity, such studies as the one we have embarked upon are open to further question and modification.

Discussion

In working with these cases, it became apparent that this was no treatment for sterility per se. No apparent improvement in fertility index could be noted. In addition, no properly controlled hormonologic studies were carried out. A few of these patients had isolated observations, but none could be considered studied adequately. This was frankly a clinical study alone, using the facilities of an open clinic and the physician's office.

Possibly, because of the long-continued use of progestin, a number of these patients who spontaneously miscarried seemed to have increased blood loss from poor immediate contraction of the uterus as well as a prolonged period of involution. Since the therapy was discontinued at about mid-term in the

majority of those cases who carried to term, presumably uninhibited estrogen effect was operable at delivery, i.e., irritability of the uterus and subsequent proper involution. It might have been well to have added estrogen therapy in the cases of pathologic ova with inevitable abortion in order to prevent this slight problem. Practically, it seems hardly worth while, and it would have added another variable. No prolonged maintenance of a pathologic ovum or dead baby was noted as due to progestin inhibition of uterine motility.

It is additionally interesting that if these cases could be urged on to another trial at pregnancy immediately after a spontaneous abortion, the statistical chances of carrying that pregnancy seemed to be enhanced. Routine curettage was performed immediately after each spontaneous abortion to guarantee complete extrusion of all products of conception. If this is done, the large majority of patients ovulate about two weeks after the abortion. It may be that even an abortive effort may prime the reproductive system for further efforts. Certainly we all have seen hypoplastic genital organs enlarge over the course of repeated abortions.

Effort was made to determine whether the patients who went into premature labor had some explainable cause for this. Of the eleven who did go into premature labor, examination of the placenta showed that there was either circumvallate formation to varying degree, low implantation, or premature separation. In other words, it would suggest that premature labor had a definite mechanical causative factor. Can it be that proper nidation, in the upper uterine segment to the proper depth, is aided?

A number of patients developed pregnancy-like changes in the breasts under therapy. There was no disorder of flow, either in character or in cycle. However, the breast changes were so frequent that they could not be used reliably in the diagnosis of pregnancy.

With the advent of more exact knowledge of the Rh factor, such a study as this must be considered in an entirely different light than that under which it was originally undertaken. If the Rh problem proves to be of importance in sequential abortions, we still have no effective therapy to combat the serologic problems. True, if the anti-Rh titer rises, one may induce labor to avoid fetal death in utero. However, such a study as this must await more information from this new field.

Summary

A brief report has been prepared investigating the use of progestin alone in the treatment of habitual abortion. By definition, habitual abortion is limited to those cases who have had at least three sequential abortions. Effort has been directed to the preconceptional phase of pregnancy, rather than to attempt to delay or to prevent abortion once it is threatened. This has been a clinical and statistical report, without adequate hormonologic control. It is a small series of cases, and so is subject to further investigation in much larger groups of cases. Results are encouraging.

There is no reason that this regimen should not be applied to any patient who has had a previous spontaneous abortion, whether progestin is used alone

or in combination with other agents. However, one should be extremely reluctant to give or to accept credit for the successful outcome of that subsequent pregnancy.

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THE ORAL USE OF HEXESTROL FOR ESTROGEN DEFICIENCY

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MANY of the synthetic estrogenic substances which have been discovered are found to be effective when taken orally. One of these preparations, diethylstilbestrol, has been given extensive clinical trial; others are being accepted and prescribed with increasing frequency. It seems certain that, in the future, additional estrogenic drugs will be produced by chemical synthesis.

Outside of their common quality of being estrogenic, these artificial hormonal drugs differ not only in their qualities of potency, absorption rate, and duration of effect, but in the degree and type of their toxic reactions. The latter untoward manifestations are receiving intensive study at the present time, and hexestrol, a synthetic estrogenic substance,^{4, 5, 7} was found to cause fewer and milder detrimental effects than diethylstilbestrol. Hexestrol proved to be especially beneficial in the treatment of the menopause patient who is relieved of hot flushes and many other climacteric symptoms.^{1-3, 6, 8-10, 16-18}

Ninety patients suffering from the menopausal syndrome were treated with hexestrol for the purpose of making a clinical comparison with other orally administered natural and synthetic estrogens. Previously, 502 patients had been treated with either diethylstilbestrol dipropionate, estradiol benzoate, or estrone;¹² 138 patients were given conjugated estrogens-equine;¹³ 47 patients and 80 patients were observed while using ethinyl estradiol and alpha-estradiol, respectively.¹¹ Thus, the effects of various estrogenic substances were observed on 857 patients and a clinical comparison was made with the 90 patients treated with hexestrol.

The hexestrol* used in this study consisted of uncoated 0.2 mg., 1 mg., and 3 mg. tablets. These tablets were scored so that they could easily be broken into two equal parts. Whenever possible, the daily dose was divided so that the substance could be taken more frequently, that is, two or three times daily.

The efficacy of treatment with hexestrol was judged by the amount of clinical improvement noted. As the hot flush was considered to be the outstanding characteristic of natural or artificial menopause, the duration, frequency, and intensity of this symptom were considered to be the most important factors in determining the degree of improvement. After this, all the other symptoms, including laboratory tests showing evidence of estrogen deficiency, were considered. Sedatives were not administered during treatment.

Clinical Material

Of the 90 patients treated with hexestrol, there were 32 patients with natural menopause (climacteric), 25 with artificial menopause, and 33 with other conditions and an associated ovarian deficiency. A few of these patients had preliminary hormone assays made of the urine.¹⁴

The patients in the climacteric period ranged in age from 38 to 59 years, and, of these, 16 were still menstruating, 3 regularly.

*The hexestrol tablets were obtained from The Wm. S. Merrell Company of Cincinnati, Ohio.

The ages of the patients with artificial menopause varied from 29 to 63 years. Bilateral oophorectomies had been performed on 6 patients, subtotal hysterectomies on 6 patients, and oophorohysterectomies on 9 patients. One of these patients was treated with radium because of metrorrhagia and to produce artificial menopause; 2 others were treated with x-ray therapy, and a fourth patient had x-ray therapy preceding bilateral oophorectomy.

Thirty-three patients with other conditions associated with ovarian deficiency were aged 15 to 46 years. This group included the following conditions: secondary amenorrhea, 5 patients; primary amenorrhea, 1 patient; oligomenorrhea, 7 patients; menorrhagia and metrorrhagia, 3 patients; dysmenorrhea, 2 patients; congenital absence of sex organs, 2 patients; frigidity, 1 patient; sterility, 1 patient; and hypoplastic breasts, 3 patients. There were 7 patients with psychoneuroses, and one with psychosis who had been given hexestrol as a therapeutic test to rule out estrogen deficiency as a cause of the symptoms.

Results

Table I shows the relief obtained from symptoms of the natural menopause with the largest dose of hexestrol used. Many patients were given medication that differed quantitatively from the dosage administered to others and the percentage of relief was estimated for each one. The varying doses which afforded the same percentage of relief were added together and the sum divided by the number of patients treated. In this way, it was possible to obtain the average daily dose required to give the percentage of relief indicated in Table I.

Table II shows the symptomatic relief obtained in the artificial menopause patients with the largest daily dose used.

Table III shows the improvement obtained in estrogen deficiency symptoms in other conditions, and Table IV shows the largest dose given to each patient.

TABLE I. NATURAL MENOPAUSE

Per cent improvement	20-40	50-60	75-85	90	100
Average dose (mg.)	0.4	0.7	1.5	1.6	2.3
Number of cases	2	3	8	6	13

TABLE II. ARTIFICIAL MENOPAUSE

Per cent improvement	0	20-40	50-60	75-85	90	100
Average dose (mg.)	0.2	0.5	0.8	1.5	2.1	2.5
Number of cases	2	1	3	5	5	9

TABLE III. OTHER CONDITIONS

Per cent improvement	0	20-40	50-60	75-85	100
Number of cases	12	6	4	3	8

TABLE IV. OTHER CONDITIONS

Largest daily dose (mg.)	0.2	0.4	0.6	0.8	1.0	2.0	3.0	6.0	9.0	12.0
Number of cases	6	1	4	1	6	1	4	1	5	4

Some of the beneficial results observed after treatment with hexestrol were manifested in improved secondary sex characteristics. Patients noted greater fullness and tenderness of their breasts or that the nipples were more sensitive. A few patients stated that there was an increase in vaginal moisture and secretion. Vaginal smears during effective treatment disclosed an improvement in vaginal cell cornification. Several patients experienced increased libido; one patient declared that the tablets were "too sex stimulating."

Toxic Reactions

The unfavorable reactions due to hexestrol therapy varied with the dosage. They appeared while six patients were taking the drug, as follows: nausea and anorexia with 1.0 mg., none with 0.25 mg.; nausea with 4.5 mg., none with 1.2 mg.; nausea with 1.0 mg., none

with 0.5 mg.; nausea and rash with 12.0 mg.; asthenia and rash with 1.0 mg.; and rash with 1.0 mg. The latter reaction came on after two months of medication. The dosages given above constituted the total daily dose for each patient.

There were two questionable reactions. One patient complained that 0.4 mg. caused facial acne, and another patient stated that hexestrol became "too stimulating" to the nervous system. This latter patient had taken 0.5 mg. for six months and, at the time of her complaint, examination showed that she did not require further medication.

The incidence of toxic reactions was not very high, since there were but 6 of the 90 patients who experienced unfavorable effects from treatment with hexestrol (6+ per cent). When the dose was decreased, three of the patients having nausea became symptom free. The other three patients developed a rash and treatment was discontinued, but they might have been able to tolerate smaller doses of hexestrol with beneficial results. However, with the above method, the treatment was discontinued in 3+ per cent of the patients.

The toxic symptoms that did occur were very mild, did not interfere with the patient's routine activity, and disappeared a few days after treatment was discontinued. No morbid sequence or evidence of permanent harm was observed; none of the patients developed a malignant growth during the period of observation.

Menstruation

There was one patient with primary amenorrhea, one with oligomenorrhea due to delayed puberty, five with secondary amenorrhea, all of whom improved, and fairly regular catamenia were established. Hexestrol was used for its estrogenic effect, and then pregnenolone (oral progesterone) was given, 5.0 mg. daily to each of the seven patients. The respective dosage of each of the seven patients differed as follows: hexestrol, 3.0 mg., 6.0 mg., 6.0 mg., 9.0 mg., 9.0 mg., 12.0 mg., and 12.0 mg. daily. Both pregnenolone and hexestrol were given during the last half of the menstrual cycle, but in some instances hexestrol was given from the fifth to the twenty-fifth day, and the pregnenolone from the eighteenth to the twenty-eighth day of the cycle. Although these patients showed some evidence of estrogen deficiency, it is possible that menstruation might have been established after therapy with pregnenolone alone.

In one patient, menorrhagia and metrorrhagia improved with the 1.0 mg. daily dose; and in two patients, one with severe cramps, the 9.0 mg. daily dose was efficacious. Hexestrol was given to these three patients from the fifth to the twenty-fifth day of the menstrual cycle. A patient with metrorrhagia took 12.0 mg. of hexestrol daily, but the bleeding persisted.

The menstrual changes were considered undesirable in five patients who were taking approximately 1.0 mg. of hexestrol daily. The treatment produced oligomenorrhea in two patients who had previously been normal, whereas the third patient menstruated four days late with severe cramps. In a fourth patient with hitherto regular menses, the medication induced prolonged bleeding, whereas the fifth patient experienced a scanty menses lasting one week, although she had not menstruated previously for six years. This last patient was the only one of eighteen patients in the natural menopause in whom bleeding was produced.

Discussion

Hexestrol was effective when administered orally. Its use thus obviated the disadvantages of hypodermic medication.¹⁵ It was a potent estrogen and relieved the patient of hot flushes and other menopausal symptoms; furthermore, it was used successfully as a therapeutic test to differentiate menopausal hot flushes from the vasomotor instability and diaphoresis of the psychoneurotic woman.

Satisfactory relief of climacteric symptoms was obtained with hexestrol in 1 to 2 mg. doses per day in the average patient in this series. Some patients required a larger dose, while others were relieved with 0.5 mg. Crotty, Schloss.

and Lyford⁶ stated that the usual maintenance dose was 1.0 mg. daily. However, Freed⁹ and Greenhill¹⁰ believed that 2.5 mg. to 5.0 mg. was a satisfactory daily therapeutic dose.

Hexestrol, like diethylstilbestrol, was inexpensive and, in most patients, could be used in the place of the latter drug, thus cutting down the incidence of toxic reaction and the frequency of ensuing amenorrhea or undesirable uterine bleeding. However, when the inhibition of ovulation or the production of endometrial proliferation and withdrawal bleeding was considered desirable, the use of either diethylstilbestrol, ethinyl estradiol, or possibly conjugated estrogens-equine was considered the medication of choice.

Comparison of Estrogens

During the past few years, several natural and synthetic estrogenic substances were tested on groups of women¹¹⁻¹³ and the various effects produced by these substances, when administered orally were studied. Although all these drugs relieved the patient of menopausal symptoms and produced the changes in the secondary sex characteristics typical of estrogenic therapy, they varied somewhat from each other both quantitatively and qualitatively.

As an example of the quantitative differences, the minimum dose giving effective relief of menopausal symptoms ranged as follows: ethinyl estradiol from 0.02 mg. to 0.2 mg.; diethylstilbestrol dipropionate from 0.2 mg. to 1.0 mg.; conjugated estrogens-equine from 0.62 mg. to 2.5 mg.; hexestrol from 0.5 mg. to 3.0 mg. In these doses the four substances were roughly equivalent in effect to each other. The majority of patients had about 75 per cent relief from hot flushes from the following doses; ethinyl estradiol, 0.07 mg.;¹¹ diethylstilbestrol dipropionate, 0.35 mg.;¹² conjugated estrogens-equine, 1.25 mg.;¹³ and hexestrol, 1.5 mg.

Qualitative differences in the estrogenic substances were evinced by the untoward effects on menstruation as shown in Table V.

TABLE V. UNDESIRABLE MENSTRUAL EFFECTS

	HEXESTROL	CONJUGATED ESTROGENS- EQUINE	DIETHYL- STILBESTROL DIPROPIONATE	ETHINYL ESTRADIOL
Number of patients treated	75	118	157	37
Caused menstruation	1	15	5	5
Missed menstrual period	0	2	4	2
Per cent with above effects	1	14	6	18
Caused late, scanty, or profuse menstruation	4	7	information lacking	3

Only those patients having an intact uterus were included in the above tabulation. The uterine bleeding was considered undesirable because it was caused in patients who normally should not menstruate. Hexestrol was much less likely to cause or inhibit uterine bleeding than the other three estrogenic substances. The figures were low for diethylstilbestrol dipropionate because of the smaller doses used in the beginning when it was felt advisable to proceed with caution. Of course, withdrawal bleeding could have been caused with

larger doses in a much higher percentage of the patients. Reference is made to the papers previously published.¹¹⁻¹³

Toxic reactions resulted in 3 to 6 per cent of the 90 patients in this series. Diethylstilbestrol dipropionate¹² and ethinyl estradiol¹¹ had a higher incidence of adverse effects, 10 per cent and 14 per cent, respectively. However, when smaller doses of ethinyl estradiol were given, there was a corresponding decrease in toxic manifestations. The toxic reactions caused by ethinyl estradiol were somewhat similar to those resulting from diethylstilbestrol dipropionate when given in equal therapeutic doses; however, they differed greatly when compared on a basis of weight. The estrogenic substances varied, inasmuch as conjugated estrogens-equine and some other estrogenic products caused no toxic symptoms.^{12, 13} With each individual, the toxic reactions varied with the size of the dose; thus, when the dose was larger, the symptoms were correspondingly more severe. Many patients who had unpleasant symptoms from moderate to large doses tolerated small yet effective doses without consequent untoward symptoms. This modification was illustrated by the three patients suffering from nausea due to hexestrol who became symptom free when the dose was decreased to one-half or one-fourth of the original quantity.

A rough comparison, milligram per milligram, of the four most potent estrogenic substances used orally is made in Table VI.

TABLE VI. COMPARISON OF FOUR ORAL ESTROGENS

1 MG. OF EACH	HEXESTROL	CONJUGATED ESTROGENS- EQUINE	DIETHYLSTIL- BESTROL DIPROPIONATE	ETHINYL ESTRADIOL
Quantitative	Strong	A little stronger	3 to 6 times stronger than hexestrol	15 to 30 times stronger than hexestrol
Qualitative	Fairly good	Best	Fairly good	Good
Uterine bleeding	Very little	2 plus or more	3 plus or less	Strongest
Development of breasts	1 plus	2 plus or better	3 plus	Strongest
Relief from men- tal depression	2 plus or bet- ter	2 plus	4 plus	Strongest
Relief from hot flushes	1 plus	1 plus, a little stronger	4 plus	Strongest
Toxic symptoms	1 plus	0	More than with hexestrol	Most

Summary

Ninety patients with symptoms and conditions caused by estrogen deficiency were treated with hexestrol with satisfactory results. This substance had a strong therapeutic effect when given orally, and 1 to 2 mg. daily were sufficient to relieve the average patient of hot flushes. There was a low incidence of toxic reactions (3 to 6 per cent) without apparent permanent harm from the dosages used. The severity of the unfavorable effects, when they occurred, depended on the strength of the dose. The tablets were used also as a therapeutic test to help differentiate estrogen deficiency from other conditions.

Hexestrol shared with diethylstilbestrol the advantage of being inexpensive. It was suggested that this synthetic estrogenic substance would be more efficacious for the treatment of some patients than diethylstilbestrol.

A comparison was made with three other orally administered substances. It was found that the undesirable effects upon menstruation were less frequent with hexestrol therapy than with the other three substances.

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INTESTINAL OBSTRUCTION IN GYNECOLOGY

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INTESTINAL obstruction is encountered with a fair degree of frequency in gynecologic practice. A gynecologist should be an abdominal surgeon able to recognize and to deal competently with this condition. He should be able to do this himself instead of hastening at the first sign of trouble to cast his burden upon the shoulders of his colleagues in "general surgery." Such a course, common in many hospitals, is responsible for the amused and tolerant contempt with which the gynecologic service is regarded by many general surgeons, and it cannot fail ultimately to produce uncertainty in the minds of the laity. It is as true in this day of narrow specialization as when the words were first uttered that: "The man who opens an abdomen should be competent to deal with any condition that he may find within it." The gynecologist engaged in abdominal surgery must know and accept its responsibilities.

Of the cases of intestinal obstruction seen on a gynecologic service, a small number will be admitted with obstruction which has not been correctly diagnosed. In the study of any new admission, a history of failure of the bowels to move for forty-eight hours, or even less if frequent vomiting is present, should make one conscious of the possibility of obstruction and make it necessary to rule this condition out before proceeding to further diagnostic effort. If, in addition to frequent vomiting, even moderate distention is present, together with colicky pain centering in any one abdominal area, loud gurgling peristalsis, and localized tenderness, the diagnosis is clear. An x-ray film showing varying fluid levels and dilated and contracted intestinal coils is pathognomonic, provided it is taken with the patient in the upright position, but should be merely confirmatory.

It is to be remembered that obstruction can result from severe pelvic inflammatory disease, from some pelvic tumors, and that malignancy of the pelvic colon is sometimes wrongly diagnosed as disease of the left adnexa. Patients may be admitted to the gynecologic service with other erroneous diagnoses but suffering from obstruction caused by postoperative adhesions, any tumor of the intestinal tract, or strangulated hernia, either internal or external. In the case of obstruction by strangulated hernia, the absence of history or sign of hernia does not entirely eliminate the possibility, as a strangulated Richter's hernia can produce intestinal obstruction without manifesting a single external sign of its presence.

While not so frequently as in former years, the gynecologist will still see postoperative intestinal obstruction and must be alert for its recognition. Generally well-understood measures of prophylaxis against this condition serve to keep down the number of such cases, but they will continue to occur. These measures are: first, the avoidance of operation in acute pelvic inflammatory conditions; second, during pelvic operations extreme gentleness in the handling

of abdominal viscera with avoidance of massive packs, a minimum of retraction, and all the little but mighty points that make up good abdominal surgery; third, the postoperative patient who vomits more than twice should have a gastric lavage with or without the use of an indwelling tube and suction apparatus. The lower left chest should be percussed at the end of twenty-four hours and, if tympany is found, and it frequently is as high as the sixth rib, a small-caliber tube should be passed through the nose to the stomach and a suction apparatus left attached for from twelve to twenty-four hours. This should be done even though the patient appears comfortable, as the presence of this sign indicates a high degree of gastric and small intestinal distention, and vomiting within a few hours is the rule. My own opinion is that many cases of adynamic ileus and at least a few of intestinal obstruction have been thus averted.

The development of postoperative intestinal obstruction must be suspected whenever "gas pains" become too frequent and persist in spite of measures which are ordinarily helpful. If the patient indicates a fairly definite point of maximum intensity of the cramp, this symptom fairly screams for attention. The development of vomiting, loud gurgling peristalsis, and tenderness complete the diagnostic picture. The x-ray, as mentioned above, is helpful, but cannot make the diagnosis alone. One must not be misled by the passage of small amounts of feces by enemas as this may merely represent the emptying of the bowel below the point of obstruction.

The diagnosis of this type of postoperative obstruction should be fairly easy. More difficult is the diagnosis of obstruction superimposed upon an adynamic or paralytic ileus. After any abdominal operation there is usually some mild degree of gaseous distention of the stomach and intestine. This is due to a temporary paralysis of the intestinal musculature caused by operative trauma no matter how slight. If this persists beyond a day or two the distension becomes marked and vomiting ensues. This is the condition known as the adynamic or paralytic ileus. A low-grade aseptic peritonitis may coexist. Mechanical obstruction will occasionally supervene by the development of obstructing adhesions at points of kinking, or even by volvulus. Active treatment of the paralytic ileus will usually prevent the development of obstruction, but, if it fails to do so, the classic signs will gradually manifest themselves and can be recognized by careful observation, the patient being examined every few hours. As long as the distention is uniform, as long as severe cramps do not occur, and as long as infrequent quiet peristaltic sounds are heard through the stethoscope, mechanical obstruction does not exist. The x-ray again is helpful, the distension being seen to be evenly distributed and the fluid levels being absent or slight and obviously without significance. Proper treatment of paralytic ileus is by the use of the indwelling stomach or duodenal tube and the suction apparatus, the use of external heat, and the administration of intravenous glucose and salt solution. Efforts to whip up the paralyzed intestinal musculature by the use of pituitrin, pitressin, prostigmine, and similar preparations are irrational and foredoomed to failure. Likewise, the ordinary enemas are not effective, although the siphon enema may be of some slight aid if it does not distress the patient too much.

A few broad and proved principles guide the treatment of intestinal obstruction. If the diagnosis is made within twenty-four or forty-eight hours of the onset of symptoms and the patient's general condition is good, without too much distention or obvious fluid loss, operation should be undertaken at once. If the diagnosis is made later, after distention and water and chloride loss have become marked, operation must be deferred until these conditions have been improved as far as possible. Intubation, suction, and intravenous normal salt solution must be used, and the last pushed to the point of insuring a satisfactory output of urine. The Miller-Abbott or other tube long enough to extend well into the intestine should be used. These measures may be continued only so long as there is definite improvement. In some instances, improvement under these measures may continue and the obstruction be relieved, a copious liquid stool announcing this happy result. This, however, can neither be anticipated nor relied upon, and the patient should be under close and continuous observation. Unless there is definite improvement within twenty-four hours, operation should be done. There is no justification for a complacent feeling that a patient with obstruction will remain alive indefinitely under intestinal intubation and suction. There is always grave danger that a patient under the most careful observation will quietly cease to improve and slip back rather suddenly to a condition of collapse and shock, and that death will occur.

In operating for the relief of intestinal obstruction, the guiding principles again are few and thoroughly tested. What is to be done must be done as quickly as possible and with as little trauma as possible. The patient is in no condition to withstand prolonged operative procedure, and the intestinal wall can seldom be relied upon to hold sutures. The point of obstruction is most quickly found by seeking the junction of collapsed and distended bowel. If the obstructing agent consists of a single band of adhesions which can be readily divided by the knife or scissors, the problem is quickly, easily, and safely solved. If, however, the obstruction is buried in a dense mass of adhesions, decision is much more difficult. In general, one should beware of trying to separate extensive adhesions involving thick, edematous intestinal wall by digital dissection. The viability of the wall of intestine obstructed for forty-eight hours is apt to be low, and it has the distressing habit of tearing if any force is used in its manipulation. If digital dissection is attempted, the effort made should be of the gentlest. As a rule sharp dissection only should be used. If adhesions too dense to be separated are encountered, or an annular tumor at the moment is inoperable, the problem becomes one of creating an opening between the intestine above the point of obstruction and the anterior abdominal skin. Where a section of intestine fairly close to the point of obstruction can be found with a wall sufficiently viable to hold sutures, this opening may be made by suturing a large-sized catheter into the bowel by two or three purse-string sutures, or by burying an inch or so of the tube in the wall of the bowel after the method of Mayo. The point of perforation of the rubber tube should be reinforced by omentum. The tube should be brought out through a separate stab wound in the abdominal wall.

If the obstruction has gone on to the point where none of these procedures is feasible, nothing is left save to exteriorize a proximal loop of bowel, close the wound around it, and hope that the patient will live long enough for an opening to be made in it in twenty-four hours or so later. In point of fact, she seldom will do so.

After any form of enterostomy, cecostomy, or colostomy has been done, the resultant decompression of proximal bowel may permit Nature to overcome the obstruction. In such a case, the fistula will usually close spontaneously. Where the obstruction continues, the decompression will permit a later, safer, and more deliberate operation to be performed with a still later closure of the fistula if necessary.

When strangulated hernias are encountered, reduction must be accomplished without any pull on the intestine whatever. If a small segment of absolutely gangrenous bowel is found, and the formation above it is in good condition, resection and anastomosis may be done. If there is extensive damage to the proximal bowel it should be dealt with as outlined above.

A few brief illustrative case reports follows:

CASE 1.—A paralytic ileus developed immediately after cesarean section. Mechanical obstruction was superimposed upon this a few days later. Intubation and suction were instituted. Improvement was prompt and rapid. In three days the obstruction had been overcome and there was a free fluid movement of the bowels. No further operative treatment was necessary.

CASE 2.—Mechanical obstruction developed after an incomplete abortion, due to infection and a tremendous pelvic exudate. Intubation and suction, together with an active sulfonamide attack on the infection resulted in a disappearance of all obstructive symptoms.

These two cases may be added to the already long list of cases of intestinal obstruction of recent origin wherein Nature, aided by decompression from above, sufficed to overcome the lesion. The outcome of the next case, however, was not so fortunate.

CASE 3.—This patient was seen at home after four months of intermittent partial obstruction. She had been completely obstructed for two days. The condition seemed intimately associated with a large pelvic tumor. She was removed to the hospital and intubation, suction, and the administration of large quantities of fluid were begun. Improvement was rapid and continuous, and all signs of obstruction disappeared. A week later operation on the tumor was attempted. A large abscess was encountered and drained. The origin of this could not be determined at the time. The patient recovered, but a fistula persisted in the scar and from this was discharged a mucopurulent material identifying the tumor as a pseudomucinous cystadenoma of the ovary, as proved by later section. Time was allowed to elapse to enable her to regain her weight and strength, and reoperation was then advised. An attack of acute bronchitis supervened and necessitated further postponement of the operation. During this period she suffered another acute obstruction. Intubation and suction were again resorted to and she improved for thirty-six hours. She then suddenly went into a state of shock, acute circulatory collapse developed, coma ensued promptly, and she died six hours after the sudden change in her condition had become apparent.

This case illustrates the danger of persisting too long with nonoperative treatment. At some time this patient ceased to improve, and the fact was not

noticed until too late. Only under the most careful and continuous observation can conservatism be practiced, and even then disaster is always near.

CASE 4.—This patient had a moderate-sized ovarian cyst, but presented signs of acute appendicitis. Operation eight hours after the onset of symptoms revealed complete obstruction of the terminal ileum by a congenital fibrous band which formed what was in effect the neck of a hernial sac holding the terminal ileum and cecum. The band was cut and the cyst removed. Recovery was without incident.

CASE 5.—Postoperative obstruction occurred one year after operation. The patient was still in good general condition and operation was performed thirty-six hours after the onset of symptoms. Recovery was uneventful.

* These cases illustrate the fact that if the diagnosis is certain and prompt, and the patient is in good condition, operation should be done at once.

CASE 6.—Two huge ovarian cysts, one as large as a full-term pregnant uterus, the other about a third as large, were removed from this patient. Her convalescence was stormy. Paralytic ileum developed promptly. Treatment by fluids, intubation, and suction was instituted. She apparently recovered from this attack, although there was always some degree of distention. On the sixteenth postoperative day signs of mechanical obstruction appeared. Operation was undertaken with what was thought to be a reasonable degree of promptness. It revealed that the condition had existed much longer than had been thought. An unsuspected annular carcinoma of the descending colon was found to be causing the obstruction. Almost complete gangrene of the proximal intestine existed. A too-prolonged and totally unsuccessful attempt was made to deliver the tumor into the wound with the idea of exteriorizing it. A hasty cecostomy was then performed. The patient stood the procedure badly, and died three days later.

In this case the diagnosis was too long delayed, although seemingly made as soon as the symptoms were apparent. Too much operative treatment of damaged bowel was attempted. Cecostomy should have been the only procedure, and it should have been hurried as much as possible.

CASE 7.—This patient suffered from recurrent attacks of partial and complete obstruction lasting two or three days at a time for a month before entrance to the hospital. A mass was palpable in the left adnexal area, and a diagnosis of ovarian carcinoma with involvement of the sigmoid was made. At operation an immovable carcinoma of the recto-sigmoid was found with the ovary not involved. Colostomy was performed. Three months later the abdomen was again explored and the tumor removed. Anastomosis was not possible. The patient was living and comfortable eighteen months later, although it is hardly to be hoped that she is permanently cured.

CASE 8.—This was similar to Case 7, except that at the second operation it was again found impossible to remove the growth. This patient died two weeks after the second operation.

Patients with intestinal obstruction from malignant disease of the recto-sigmoid will occasionally be encountered on a gynecologic service because of an erroneous diagnosis of left adnexal disease. The gynecologist must know that the same guiding principles apply in the treatment of these cases as govern the treatment of obstruction from any other cause, with the addition of course of the general principles of the treatment of malignancy elsewhere in the body.

Summary and Conclusions

1. The gynecologist is engaged in the practice of abdominal surgery.
2. He should be prepared to accept the responsibilities of that practice and to deal adequately with its complications. To do otherwise is to cast discredit upon the specialty.
3. The recognition and proper treatment of intestinal obstruction is a responsibility of every individual who makes an abdominal incision.
4. A discussion of the diagnostic points and general principles of treatment of this condition has been made.
5. Strict adherence to these principles will do much toward keeping the mortality from intestinal obstruction to a minimum.

500 PENN AVENUE

AN EVALUATION OF THE HOGBEN PREGNANCY TEST

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THE Hogben pregnancy test, based upon egg extrusion in the South African clawed toad (*Xenopus laevis*), has been extensively used, especially in the British Empire, since the reaction was first described by Hogben¹ in 1930. Of some 5,300 tests reported by six²⁻⁷ different observers, the percentage accuracy is stated to be between 96 and 100 per cent. However, as experimental material was used by a number of investigators, no true idea can be obtained from these figures as to the accuracy of the test for routine clinical purposes. In order to obtain such a clinical evaluation, the results obtained with the Hogben test on 157 cases presenting diagnostic problems have been analyzed. An analysis of the 157 tests performed in the present series shows that they may be classified according to diagnosis in the following manner: 60 intrauterine pregnancies, 11 abortions, 2 ectopic pregnancies, 1 abdominal pregnancy, and 68 nonpregnant cases with miscellaneous diagnoses.

The method used was that described by Weismann⁸ and, briefly, involves concentration of 40 ml. of the first morning urine by acetone precipitation and the injection of 1 ml. of the aqueous concentrate into the dorsal lymph sac of the toad. Early observers used as many as 10 animals to a test. A single toad per test has been used in the present series. Ovulation occurs and eggs are extruded in from eight to sixteen hours following an injection of a specimen containing a sufficient concentration of chorionic gonadotropin. Injections are usually given in the evening and observations made the following morning. This is in order to allow the animal to remain in darkness overnight, as it has been found that light sometimes inhibits egg extrusion.⁹ A month is allowed as a resting period for each animal after a positive test, and two weeks following a negative. Landgrebe,⁶ who has had a vast experience with these toads, has used the same animals over a period of twelve years and finds no loss of sensitivity to stimulation. His records also show that each animal in his colony is used approximately ten times a year.

Sixty-eight tests were performed to exclude the diagnosis of pregnancy under the following conditions: amenorrhea associated with obesity, myomata uteri or tuberculosis, corpus luteum cysts, ovarian tumors and functional irregular vaginal bleeding. Negative responses were obtained in all 68 instances and proved to be correct in the 56 cases adequately followed. The fact that no false positive tests were obtained is in keeping with the findings in the literature for, in the 5,300 tests reported, no false positive result has as yet been recorded. Landgrebe,⁶ however, has found experimentally that a positive test can be obtained with the urine of menopausal women if the gonadotropic titer is high. This fact should be borne in mind for the interpretation of individual tests.

Sixty tests were performed on patients on whom the final diagnosis of normal intrauterine pregnancy was made. Forty-six were positive and 14 negative. Forty-one of the 46 positive tests were proved correct by follow-up studies;

the remaining five were so classified on presumptive evidence. There were no positive tests reported before the fortieth day of the pregnancy, as counted from the first day of the last menstrual period.

Eleven of the 14 false negative cases have been adequately followed, while three have been diagnosed on presumptive evidence. An analysis of these tests shows that seven, and possibly eight (Cases 1, 2, 3 [2 tests], 4, 5, 6, and 7 [1 test]) were performed when the duration of the pregnancy was under 40 days (Table I). One of these cases gave a positive rat test* although only 24 days past her last menstrual period; one had a positive Hogben test when repeated on day 40; and one had a positive Friedman and rat test on day 37; one case showed a positive rat test at day 45, one week after the negative toad test, but even at this date the value was only 130 I.U. of chorionic gonadotropin per liter of urine. Seven negative tests were obtained on patients who were more than 40 days past their last menstrual period. Of these, one showed a positive Friedman test at day 69. This patient was a 45-year-old Negro woman whose youngest child was 10 years old. On physical examination she was thought to be pregnant, but no follow-up, has been obtained. One case, tested at 72 days, also had a negative rat test. This patient has since delivered approximately on her expected date of confinement.

TABLE I. TABULATION OF DATA ON CASES GIVING FALSE NEGATIVE TESTS

CASE	DAY OF PREGNANCY	REMARKS	FOLLOW-UP
1	24	Positive rat test (urine)	Delivered
2	35	Positive rabbit test Positive rat test 30,000 I.U./liter (serum) 37 days	Delivered
3	30-40? 50-60?	Irregular menses	Fetal heart heard at about 4½ months
4	37		Delivered
5	38	Positive toad test 40 days	Delivered
6	38	Positive rat test 130 I.U./liter (urine) 45 days	?
7	39	Positive toad test 76 days	Delivered
8	44		Delivered
9	45		?
10	69	Positive rabbit test	?
11	72	Negative rat test (urine)	Delivered
12	88		15 cm. fetus at hysterectomy

In an attempt to explain the 14 false negative results, we might say that seven, and possibly eight, tests were performed before day 40 of the pregnancy; the urinary chorionic gonadotropin is not high enough at this stage of pregnancy to give consistently positive results. An additional number of poor results can be accounted for by individual animal sensitivity. It must be remembered that a single toad per test has been used and, had it been possible to use

*Delfs, E.¹⁰ The test, as originally described, measures the international units of chorionic gonadotropin per liter of blood serum by the uterine weights of immature rats. It has been adapted to urinary assays where indicated in the present study.

even two animals to a test, the results would no doubt have been improved. Case 10 is perhaps an example of this type of error as the Friedman test done at the same time was positive. Another source of error to which the test is subject is the irregularity of the chorionic gonadotropin titer in the urine. This accounts for a number of false negative tests which we have considered unavoidable and affects the Friedman and Asehheim-Zondek tests as well as the Hogben. Cases 6 and 11 illustrate this point. Case 6 showed a urinary titer of only 103 I.U. per liter at day 45 when the titer is expected to be 4,000 I.U. per liter or above by the techniques used.¹⁰ Case 11 had less than 750 I.U. per liter at day 72 when the titer should be 10,000 or above. Excretion of chorionic gonadotropin varies widely from individual to individual and from specimen to specimen in the same individual. Although it roughly parallels the blood serum gonadotropin, it does not do so exactly (Table II). The factors controlling this difference are those concerned with the metabolism or detoxification and the excretion of the hormone, and extraneous factors which destroy it in the urine after excretion.

Such errors can be obviated by using the Delfs serum technique. In our experience, no pregnancy test based upon urinary excretion of chorionic gonadotropin approaches those based upon blood serum concentration in accuracy or sensitivity. In theoretical support of such an opinion, a chart has been made showing the average serum gonadotropin values in 23 normal pregnancies compared with actual serum and urinary gonadotropin values in two early pregnancies (Fig. 1). The disadvantage of the serum technique is that it is more time consuming.

TABLE II. COMPARISON OF RELATIVE CHORIONIC GONADOTROPIN VALUES IN BLOOD AND URINE, TWO CASES

CASE	DAY OF PREGNANCY	CHORIONIC GONADOTROPIN IN INTERNATIONAL UNITS* PER LITER	
		BLOOD	URINE FIRST MORNING SPECIMEN
I	70	54,880	25,020
	76	38,620	5,290
	84	16,920	5,120
	91	40,700	2,656
II	50	43,680	10,580
	57	22,080	21,860
	64	37,000	2,500
	71	20,740	4,420
	78	9,700	
	84	11,340	610
	110	5,190	390

*Delfs, E.¹⁰

In these two groups of cases we find that of 108 tests performed and adequately followed, 11 proved to be incorrect. All of these were false negative responses. No false positive tests were obtained. This gives an over-all percentage accuracy for the Hogben test of approximately 90 per cent. However, if all cases tested under the fortieth day of gestation are eliminated, this figure is raised to 96 per cent, which is closer to the accuracy obtained with experimental material.

Eleven Hogben tests were performed on 10 cases of abortion (Table III). Six of these were positive and five negative. Two of the five negative tests were

performed on completed abortions and one on a patient who had been bleeding two days and completed her abortion the following day. The rat test performed on the same day was positive. One case had a negative toad test at day 38, while a rat test performed on the blood serum was positive. This patient miscarried at six weeks. The fifth case had a negative Hogben and a negative rat test at day 52; both tests were positive by the seventy-eighth day, and the patient miscarried on day 114.

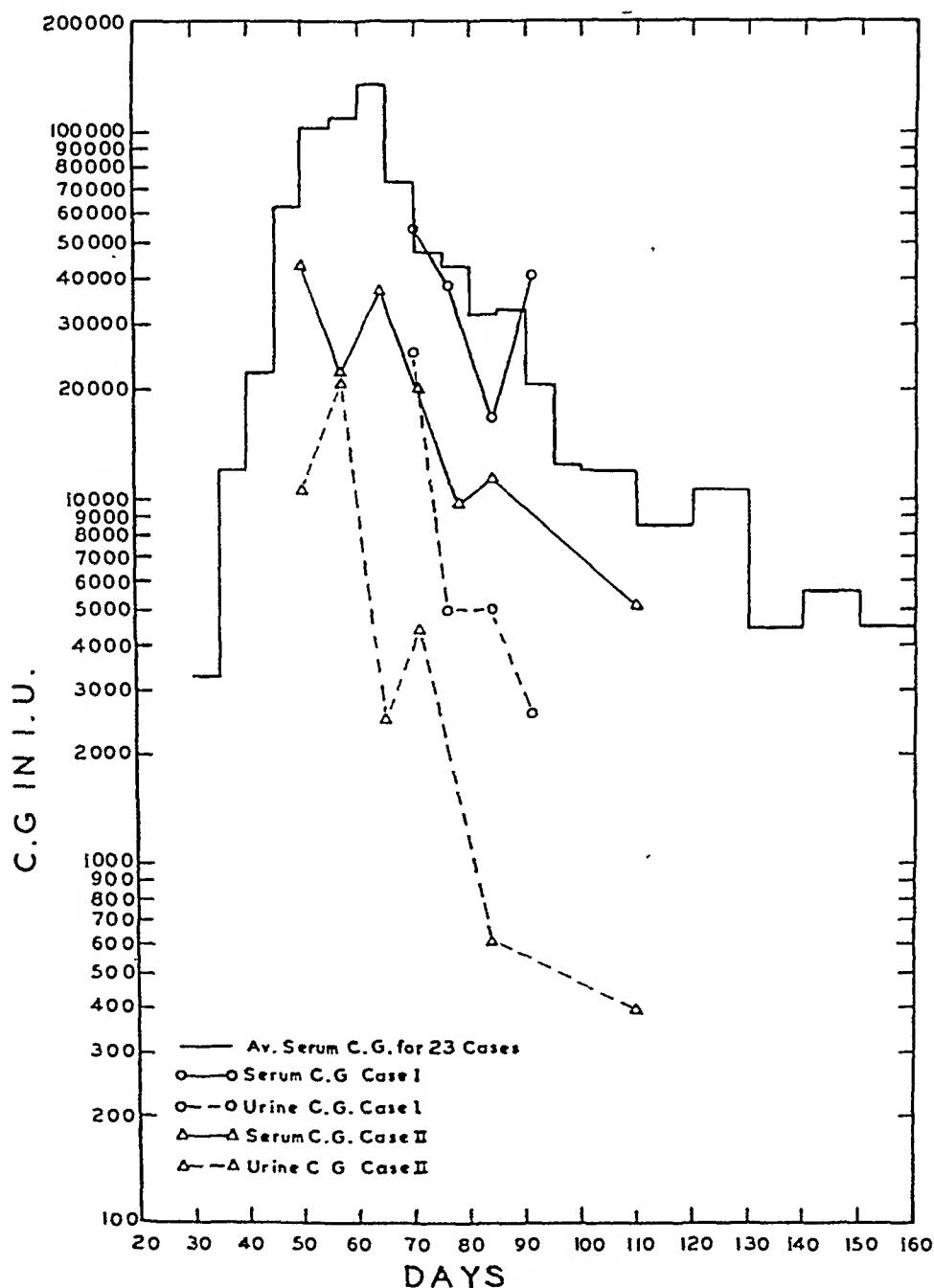


Fig. 1.—Average serum chorionic gonadotropin values for 23 normal pregnancies compared with actual serum gonadotropin and urinary gonadotropin values in two women. The chorionic gonadotropin is expressed in international units per liter of serum or urine plotted on a logarithmic scale. The days of pregnancy are calculated from the first day of the last menstrual period. The urine used represents the first morning specimen.

TABLE III. TABULATION OF DATA ON ABORTIONS AND EXTRAUTERINE PREGNANCIES

CASE	POSITIVE	NEGATIVE	ABORTED	REMARKS
<i>Abortions:</i>				
13	87 days		155 days	Bleeding throughout
			Fetus not macerated	
14	120 days		128 days	Bleeding throughout
			No recognizable fetus	
15	57 days		64 days	Gonococcal cervicitis
16	(Jan. 1-18)		(Jan. 1-24) 3½ months	
	3½ months			
17	9 days		9 days	
18		Positive rat test	77 days	
		1,230 I.U./liter (serum)		
		37 days		
19	78 days	Negative rat test (urine)	114 days	
		52 days		
20		Positive rat test	59 days	Bleeding at time completed
		More than 740 I.U./liter (urine)		
		57 days		
21		66 days	63 days	Completed abortion
22		46 days	45 days	Completed abortion
<i>Ectopic Pregnancy:</i>				
23	69 days			Ruptured
24		156 days		Dead
<i>Abdominal Pregnancy:</i>				
25		Negative rat test (urine)		Placenta partially detached
		164 days		Baby alive—963 Gm.

Only two ectopic pregnancies have been studied. One had a positive Hogben test and acute clinical symptoms. This patient was 69 days past her last menstrual period. She was operated upon immediately and a ruptured ectopic pregnancy was found. The second case had a negative Hogben test and the clinical symptoms were minimal. She was 156 days past her last regular menstrual period. Two months after the negative toad test she was operated upon because of persistent pain, and a resorbing tubal mass with an organized pelvic hematoma was found. Microscopic examination of the tubal mass showed the presence of the hyaline and shadow chorionic villi.

One case of abdominal pregnancy studied gave a negative Hogben and rat test. At operation the placenta was almost completely detached; this may explain the low urine chorionic gonadotropin values. The placenta, however, was normal in appearance, and the baby lived eight hours.

Conclusions

In conclusion, it would seem from the present study that a normal intra-uterine pregnancy cannot be diagnosed by the Hogben test with any accuracy before the fortieth day of gestation. Following this period the expected accuracy approaches 96 per cent. Approximately two-thirds of threatened or incomplete abortions will give positive Hogben tests. Cases of corpus luteum cysts, suspected of being ectopic pregnancies, give negative reactions.

These results are comparable with those obtained with the Friedman test and show the Hogben test to be a satisfactory one for clinical use. The most important clinical advantage of the Hogben over the Friedman test, aside from technical superiority in the laboratory, is that it gives no false positive results.

Animals were obtained from The Jay E. Cook, Xenopus Importer Company, Baltimore, Md.

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Addendum

Since writing the present paper an additional 100 tests have been performed with a 95 per cent accuracy. The Scott technique⁵ was used in this group of assays and no test has been invalidated by death of the toad.

A POSSIBLE HEPATIC (HEPATORENAL) FACTOR IN GYNECOLOGIC MORTALITY

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ALTHOUGH it has been realized for a number of years that so-called "liver" and "liver-kidney" deaths (liver failure, hepatorenal syndrome) can follow any variety of surgery, not a great deal of attention has been paid to their possible occurrence after gynecologic operations. Heyd's¹ original report, in 1924, dealt chiefly with surgery of the biliary tract but mentioned liver failure after pancreatic and gastrointestinal operations. Since then, this type of death has been reported in association with intestinal obstruction, thyroid disease, and burns, and following such operations as radical mastectomy, splenectomy, and thoracoplasty.² Its occurrence after gynecologic operations, however, seems to have been mentioned only by Martin,³ Connell,⁴ and DeCourcy.⁵ One of Connell's cases was an operation for ovarian cyst; the remaining cases were associated with hysterectomy.

The late Hilliard E. Miller,⁶ in an analysis of 404 recent gynecologic deaths at Charity Hospital of Louisiana at New Orleans, called attention to a small group in which liver failure or the liver-kidney syndrome seemed to be responsible for the fatality. In an investigation of the postmortem material at the same institution for the years 1937 to 1940, inclusive, I have identified 10 deaths following gynecologic surgery, in which this cause seemed to be entirely responsible or in which the necropsy findings suggested that hepatic failure played an important part in the fatal outcome. A considerably larger number of cases of the same kind were discarded because the intrusion of other factors reduced the importance of the hepatic factor.

Analysis of Cases

Six of the 10 patients in this series were Negroes, whose respective ages were 27, 38, 41, 42, 48, and 58 years. The ages of the four white women were 26, 42, 43, and 47 years. All were submitted to hysterectomy, one by the vaginal route, four by the supracervical technique, and the remainder by the complete technique. Three operations were performed under spinal analgesia and the remainder under ethylene-ether anesthesia. Six operations lasted less than an hour; the others lasted, respectively, 90 minutes, 95 minutes, 2 hours and 5 minutes, and 2 hours and 10 minutes.

Three patients were in poor condition when they were first seen, because of prolonged vaginal bleeding, but they were transfused before operation and were regarded as presenting good risks. Another patient, 58 years of age, was hypertensive and had cardiac disease, but she was well compensated and a medical consultant considered operation safe. This patient had an enlarged liver, and hepatomegaly was also observed in another patient, a 36-year-old white woman. Two patients were rather poorly nourished and three were obese.

One patient died on the table at the conclusion of the operation, and one death occurred on the sixth day. The remaining deaths occurred between 8 and 72 hours after operation. In every instance death was unexpected and in several instances it was almost catastrophic.

With a single exception, to be discussed later, in which active hemorrhage was found, the outstanding postmortem findings in all of these cases were hepatic or hepatorenal changes, ranging from cloudy swelling to frank necrosis. Fatty metamorphosis was present in a number of instances, and in three was grossly evident.

In addition to the hepatic and hepatorenal changes mentioned, minor, nonlethal pathologic changes were observed in several cases. One patient had 200 c.c. of bloody fluid in the peritoneal cavity, one had a small localized area of pelvic peritonitis, and two had microscopic areas of atelectasis.

Comment

The concept of possible hepatic or hepatorenal failure after surgery is still doubted by some surgeons, chiefly, as certain writers rather bitterly point out, by those who have never experienced the disaster. On the surface, however, there seems no more reason why deaths should not occur from this cause than from cardiac failure or renal failure *per se*.

Clinically this type of death takes two forms. In the first, or so-called "liver death," the patient is as likely as not to be a good or fairly good risk, but he reacts slowly and sluggishly from anesthesia, his appearance and behavior are lethargic, the temperature begins to rise alarmingly shortly after operation, and death occurs within 8 to 72 hours, with extreme hyperpyrexia and a rising pulse rate dominating the clinical picture. In the second type, the so-called "liver-kidney" death or hepatorenal syndrome, the postoperative course is fairly normal for four or five days, or even longer. Then, in spite of an increased fluid intake, oliguria progresses to anuria and death clinically seems to be due to uremia. The hyperpyrexia noted in liver deaths is absent. If blood chemical tests are made, the nonprotein nitrogen and urea nitrogen, which were normal if tested before operation, are found to have risen to high levels.

Postmortem examination reveals little to explain why death has occurred. In liver deaths there are various degrees of degeneration in the liver cells. In liver-kidney deaths the same changes in the liver are present and there are also degenerative changes, sometimes progressing to necrosis, in the convoluted tubules of the kidney.

In essence, the most reasonable theory^{2,7} advanced to explain liver and liver-kidney deaths is as follows: Since any form of anesthesia has some effect on the liver, a certain fall in hepatic function can be expected after operation, even in young and healthy subjects submitted to simple surgery. The damage is accentuated by prolongation of the procedure and anesthesia, the trauma of surgery, blood loss, and the toxic effects of death of tissue. Furthermore, as demonstrated by Crile,⁶ the mere opening of the abdomen causes a reduction in the temperature of the liver, a 10 per cent decrease in chemical activity resulting for every 1 degree fall in temperature.

The sum of these various factors is of little consequence in persons with intact livers, and is, indeed, survived by the majority of persons whose livers are damaged, particularly if they have been well prepared for operation. The liver is a highly adaptable organ, with multiple functions, and experimental

evidence⁹ shows that it can continue to function when it has been damaged as much as 80 per cent. A damaged liver, however, which is already the site of functional and structural alteration, may be so gravely affected by the considerations listed as to undergo further damage. Eventually it may become unable to cope with its normal physiologic function of detoxifying the toxic substances which reach it in the course of normal body metabolism. As the hepatic cells become increasingly unable to fulfill their normal function, they themselves undergo necrotic changes and the circulation is presumably filled with the undetoxified substances which the liver has been unable to handle, as well as with the toxins of the necrosing hepatic cells. At this point the toxemia may be so overwhelming that the so-called liver death occurs.

If, however, the patient survives the toxemia, the failing function of the liver is taken over by the kidney, the next great detoxifying organ of the body, as a purely physiologic routine. But the kidney is not physiologically fitted for the whole task of detoxifying the normal products of body metabolism, quite apart from the toxic substances elaborated in the liver. It breaks down in its turn, and the overwhelming toxemia kills the patient in the second, or hepatorenal, phase of the syndrome.

The theory outlined has been advanced by Helwig and Schutz⁷ and by Boyce.² The only point of difference between these observers is that the former believe that some potent toxin elaborated in the necrotic hepatic tissue has a specific effect upon the renal parenchyma, while Boyce does not believe it necessary to postulate a specific action.

Death in cases in which the liver is known to be seriously damaged is not difficult to comprehend. Much more difficult to accept is what Robertson and his associates¹⁰ described as a "certain unexplained surgical mortality," which is attributed by a number of observers to what has been termed a "state of hepatic inferiority." Hepatic inferiority was, I believe, the background of 7 of the 10 gynecologic deaths which have just been analyzed. Some individuals, as Henschen¹¹ pointed out, are born "liver weaklings." Others acquire hepatic inferiority in the course of living, just as cardiac or renal inferiority develops. The numerous writers who advance this concept base their evidence partly upon the finding of unexpected pathologic changes when biopsy of the liver is performed for any reason, and partly upon the unexpected hepatic dysfunction revealed by functional tests. Boyce² and Rozendaal and his associates,¹² among others, have emphasized the entirely unexpected hepatic dysfunction sometimes found even in young persons, and the latter group of authors observed pessimistically that the only reason the percentage of dysfunction in their series was as low as 29 per cent was because so many of the patients had not yet had time to develop dysfunction. If their observations are accepted as valid, it is not unreasonable to assume that these patients present poor prospects for surgery, in the process of which their already deficient hepatic function may be depressed to nonviable levels, particularly because they are usually regarded as presenting good risks and are seldom prepared in any way for operation.

An experimental observation recorded by Boyce,² who, incidentally was able to reproduce the liver-kidney phase of this syndrome experimentally, is worth citing as illustrative of the theory just outlined.

At laparotomy on a large, vicious dog several small ecchymotic areas between the gall bladder and hepatic parenchyma were observed and were found to have been caused by a blow used to control the animal while it was being prepared for operation. Cholecystectomy and common duct ligation were rapidly performed under ether anesthesia. The dog was on its feet and moving about within fifteen minutes, but died at the end of twelve hours. Post-mortem examination revealed the liver to be pale, swollen, and finely mottled, and histologic examination showed many areas of hyperemia and necrosis. The kidneys were grossly normal but histologic examination showed areas of cloudy swelling of the tubal epithelium. There was no other cause of death.

Boyce derived two lessons from this experience: The first was the rapidity with which apparently insignificant hepatic damage can be translated to a lethal degree under an additional strain, just as individuals with minimal hepatic damage are perhaps put in jeopardy when they are submitted to surgery. The second lesson was the ease with which fatal potentialities can be overlooked. He and his associates had been studying hepatic damage for at least five years, yet the lethal possibilities in this instance escaped them completely until the animal's totally unexpected death twelve hours after operation.

Those lessons seem definitely applicable to the ten cases in this small series. None of the patients had any tests of hepatic function prior to operation and, except for the patients transfused to replace actual blood loss, none of them had any preoperative preparation. The hepatomegaly present in two instances was entirely ignored. The possibility of liver failure was not suspected in a single instance after operation, though in several instances the clinical diagnoses seem to have been made in desperation, so entirely were they at variance with the clinical findings.

One patient, for instance, whose temperature rose to 103° F. the day of operation and to 104.2° the following day, escaped bronchoscopy only because she refused to submit to it. Death occurred forty-four hours after operation, and the clinical diagnosis was peritonitis, of which there had been no clinical evidence, versus atelectasis, of which there had also been no clinical evidence. At necropsy the peritoneal cavity was clean, and the atelectasis present was demonstrable only in a limited area and by microscopic examination. The liver weighed 970 grams, and both grossly and microscopically showed fatty changes, the normal lobular arrangement being completely obliterated. The convoluted tubules of the kidneys were swollen and showed slight granular changes; the glomeruli were intact.

In another case the clinical cause of death was set down as embolism versus atelectasis, but autopsy revealed neither condition. A few cubic centimeters of serosanguineous fluid in the peritoneal cavity was specifically stated not to be a true exudate, and there were no other positive findings except in the liver and the kidneys. The liver was grossly lighter than normal and slightly mottled, and microscopically showed marked parenchymatous degeneration. The kidneys were grossly normal and microscopically showed mild parenchymatous degeneration of the convoluted tubules.

In two cases death was attributed clinically to the anesthetic agent. In one case, in which death occurred at the conclusion of an operation lasting forty-five minutes and performed under ether anesthesia, the liver weighed 900 grams and was extremely soft. Microscopic examination showed marked granular changes in the cytoplasm of the polygonal cells. It does not seem unreasonable to assume that this patient, judging from the size and consistency of the liver, had a high degree of hepatic damage before operation, which was aggravated to the lethal degree by the anesthesia.

The second death attributed to the anesthetic agent occurred seven hours after operation, as the result of "sensitivity to novocaine." Analgesia was not satisfactory and was

supplemented by nitrous oxide. The operation lasted ninety-five minutes. The patient stopped breathing in the course of the procedure and was given artificial respiration for twenty minutes. Her blood pressure fell from 200/100 to 100/70 and remained low. She had bled from the vagina for a long period before admission to the hospital, and even after transfusion her red blood cells numbered only 3,500,000 per cubic millimeter. A moderate degree of edema of the brain and spinal cord was found at necropsy, and undoubtedly played a part in the fatality, but the hepatic findings were much more striking. The liver, which weighed 1080 grams, was so soft that it flattened out immediately when it was placed on the dissecting board. It was pale yellow, the natural markings were obliterated, and microscopic examination showed marked parenchymatous degeneration. The kidneys were normal. In this case the chain of events seems to include some degree of hepatic damage before operation, aggravated at operation by inadequate oxygenation, both because of the fall in blood pressure and because of the respiratory difficulties. The studies of Shaw, Steele, and Lamb¹³ on anoxemia in spinal analgesia support this point of view.

One patient, as already noted, unquestionably died of postoperative hemorrhage, which was the major cause of death. The liver, however, was found at necropsy to be light grayish-brown and very soft, and normal markings were absent. Microscopic examination showed many small areas of necrosis, swollen hepatic cells, and obliteration of the sinusoids. The patient died twelve hours after operation, and it seems unlikely that such extreme hepatic changes could have occurred in so short a time. On the other hand, it seems quite reasonable that they could have been caused by preoperative damage, aggravated by the falling blood pressure at operation (94/70), and the subsequent hemorrhage, with resultant anoxemia.

The three obese patients in this series should be specially mentioned, for obesity, as Ravdin and his associates¹⁴ have pointed out, tends to be associated with increasing concentrations of hepatic lipid. The patients in their series who were of average weight were found to have 3.9 per cent of hepatic fatty acids. Those with 1 plus obesity had 4.6 per cent, those with 2 plus obesity 6.4 per cent, and those with 3 plus obesity 10.3 per cent.

The age of the patients in the series also should be emphasized. With a single exception, the range was 36 to 58 years, and the high level bears out Boyce's² theory that patients with damaged livers are affected adversely by the mere act of living. He attributed the high percentage of liver damage which he observed in nodular goiters in Negroes to the fact that this type of goiter occurs in older patients, and that life, as a rule, goes harder with Negroes than with white patients.

Therapeutic Measures

Whether or not the liver played a major role in the ten fatalities in this series, postmortem observations show that it played an important role, and it is significant, as already pointed out, that neither before nor after operation was the possibility of hepatic failure suspected. The lesson is obvious. This possibility should be considered as an explanation of unexpected and inexplicable postoperative complications, and, more important, should be guarded against by adequate tests and adequate preparation before operation.

The situation is by no means as gloomy as the observations of Rozendaal and his associates¹² would indicate. For one thing, the capacity of the liver to endure insult is enormous, and the number of patients likely to die of liver failure after operation is small, even in the absence of adequate preparation. For another, though tests of hepatic function are still far from satisfactory, they are surprisingly useful in indicating those who need special preparation. Graham's¹⁵ record in this respect is notable. On the basis that abnormal (50 per cent or more) dye retention indicates hepatic damage, he was able, by proper

preoperative preparation, to reduce his mortality for cholecystectomy over a three-year period from 6 per cent to 0.5 per cent, and his mortality for common duct surgery from 7.7 per cent to 2 per cent. Althausen and his associates,¹⁶ by routine use of hepatic function tests, were able to reduce the mortality of biliary tract surgery at the University of California Hospital from 10 per cent to 2 per cent. Hepatic damage is, of course, much more frequent and usually much more extensive in disease of the biliary tract than in gynecologic disease.

In occasional cases hepatic damage is irreparable, and in other cases it is difficult to repair. In most cases, however, correction is reasonably simple. The administration of dextrose, preferably by the oral route whenever it is possible, a diet high in protein, the maintenance of a satisfactory fluid balance, and the use of plasma and whole blood as indicated are all that is necessary. Most patients, as a matter of fact, do not need such a regimen. A properly balanced diet, liberal fluids and additional dextrose in the form of sweetened drinks, hard candies, and jelly¹² are all that is necessary. Elaborate methods of preparation are seldom omitted when they are indicated, and it seems ironical that simpler measures, which are adequate in many cases and a wise precaution before any type of surgery, are usually omitted.

Ravdin and his associates¹⁴ have recently established the value of a special preoperative diet, containing adequate calories and consisting of at least 74 per cent of carbohydrate, not over 6 per cent of fat, and at least 20 per cent of protein. Patients with severely damaged livers who were not prepared by this diet showed an average lipid hepatic content of 14.8 per cent, whereas those prepared with it showed a lipid content of only 4.2 per cent. The glycogen content of the liver in the prepared group was 3.3 per cent, as compared with a content of 2.8 per cent in an unprepared control group with microscopically normal livers. These observers believe that such dietary preparation is so important for patients with damaged livers that if the palatably prepared diet is not taken by mouth, it is administered by stomach tube.

All of the patients who survived operation in the small series of gynecologic deaths reported in this paper had adequate postoperative therapy, including infusions, transfusions, and inhalations of oxygen. As a matter of fact, the postoperative treatment of gynecologic patients at the New Orleans Charity Hospital is almost uniformly good. Yet, as Miller⁶ pointed out, the mortality of surgery for fibroid tumors has been reduced to so low a level that there is a tendency to view all cases with complacency and to operate without proper preoperative preparation. Complacency seems the basic reason why most of these deaths in this series occurred, and a study of the cases suggests that uneasiness in respect to the liver might be a wholesome improvement in the preoperative study of the patients to be submitted to gynecologic surgery. Even if functional tests of the liver are not practical routinely, because of the volume of clinical material to be handled, preparation with diet, a liberal intake of carbohydrates and protein, and attention to the fluid balance could be carried out for 48 to 72 hours in ambulatory patients before hospitalization and would not tax hospital facilities. The number of liver and liver-kidney deaths is small, but could be further reduced by this means. The aim of this communication is to call attention to the possibility of such a reduction.

Summary

The possibility of the occurrence of the so-called "liver" and "liver-kidney" deaths after gynecologic surgery is discussed. The theory of "hepatic inferiority" and the "liver weakling" is also discussed. Ten deaths after gynecologic surgery are analyzed, and it is pointed out that in them a liver factor was an important cause of the fatality, and sometimes the only cause. A method of preventing such deaths is briefly outlined.

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AN EVALUATION OF THE GUTERMAN PREGNANCY TEST

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THE role of progesterone in the physiology of menstruation and reproduction has been well established.^{1, 2} The isolation of pregnanediol,³ the end product of progesterone metabolism, and the development of biochemical assay for this compound⁴ has made it possible to obtain a quantitative measure of the functional activity of the corpus luteum. Pregnanediol, in the form of its acid-hydrolyzable complex, sodium pregnanediol glucuronide, is found in the urine of nonpregnant women during the luteal or postovulatory phase of the menstrual cycle. If impregnation occurs, the compound is found continually in increasing amounts until parturition. Quantitative studies of the excretion of pregnanediol in the urine of pregnant and nonpregnant women have been reported by a number of workers.⁵⁻¹⁰

The increased excretion of sodium pregnanediol glucuronide in the urine of pregnant women has been used for the early diagnosis of pregnancy by a number of investigators.^{5, 6, 11, 12} Most of these methods depend upon gravimetric determination of pregnanediol by the methods of Venning⁴ or of Astwood and Jones.^{13*} Talbot and co-workers¹⁴ have developed a colorimetric assay method based upon the color complex developed by free pregnanediol when dissolved in concentrated sulfuric acid, as originally described by Kober.¹⁵ This reaction was shown by Zimmermann¹⁶ to occur also with certain 17-ketosteroids. Guterma¹⁷ has recently attempted to combine the methods in effecting a rapid and accurate pregnancy test.

The Guterma test depends upon the isolation of pregnanediol by a modification of the procedure devised by Astwood and Jones, followed by the addition of concentrated sulfuric acid to the dried compound. A colorless to yellow solution is read as negative, and an orange to brown solution is considered to be indicative of pregnancy. A positive color reaction results, according to Guterma, when 1 mg. or more of free pregnanediol is present in 100 ml. of morning urine. It is his contention that the presence of a positive color reaction in the presence of amenorrhea indicates a normal pregnancy.

It has been demonstrated that the excretion of sodium pregnanediol glucuronide during the luteal phases of normal nonpregnant women varies from day to day and from patient to patient.^{5, 6} This is apparently dependent upon the functional activity of the corpus luteum of the particular cycle observed and the efficiency of the metabolic and excretory mechanisms.⁶

*In the Guterma modification of Astwood and Jones' procedure, one precipitation is omitted. This step, which also involves washing with petroleum ether, removes any 17-ketosteroids which have been coprecipitated with the pregnanediol.

The purpose of the present experiment is to evaluate the Guterman test. The cases studied included normal nonpregnant women, early pregnancies, conditions simulating or likely to be confused with pregnancy, and normal males.

Method

First morning specimens are used in all cases. These are collected over 1 to 2 Gm. of sulfanilamidé as a preservative, and specimens are kept refrigerated until used. At no time is this period longer than seventy-two hours.

The technique employed is that described by Guterman with slight modifications for convenience in this laboratory and with the addition of a colorimetric procedure.

In all cases where an electric hot plate is specified by Guterman, vacuum distillation over a steam bath is substituted, with the exception of the original hydrolysis where a Bunsen flame is employed.

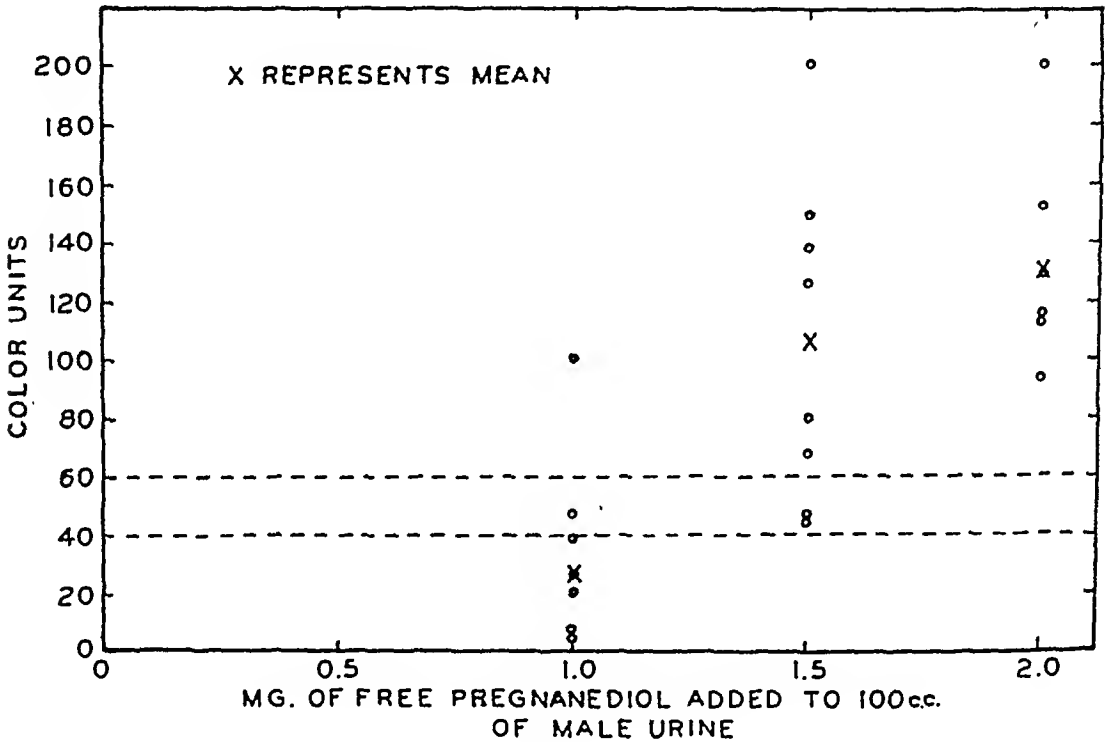


Fig. 1.

In step B-3, 1 ml. of a 20 per cent solution of sodium in 95 per cent ethanol is used in place of 20 ml. of 10 per cent sodium hydroxide.

In step B-5, filtration by gravity through No. 42 Whatman paper is used instead of a fritted glass filter.

In step D-1, filtration through No. 42 Whatman paper in a 3 cm. Büchner funnel is used instead of a fritted glass filter.

Colorimetric Procedure.—This step is added because of the difficulty encountered in measuring the color shades by direct observation, particularly in borderline cases.

A color standard is prepared which exactly matches in the Klett photoelectric colorimeter the color obtained when male urines are subjected to the procedure. This is a potassium dichromate solution of 3.42 Gm./1 concentration. A filter having a transmission range of 500 to 570 millimicrons is used. With standard in-place, the galvanometer is balanced with the dial at zero by adjusting the diaphragm. The standard is then replaced by the sample in a colorimeter tube, and the galvanometer balanced with the resistance dial. The dial reading is recorded directly, and results are expressed in terms of the dial reading or "color units" (C.U.).

The color units are standardized, as shown by the graph (Fig. 1) from the readings given by prepared samples of male urine to which known amounts of sodium pregnanediol glucuronide are added. We consider 40 to 60 C.U. as the range of transition between positive and negative; all values above this band are orange to brown, and those below are yellow. Quantitatively, this zone represents 1.0 to 1.5 mg. of free pregnanediol per 100 ml. of urine. This is the same transition point used by Guterma in judging his samples by direct vision.

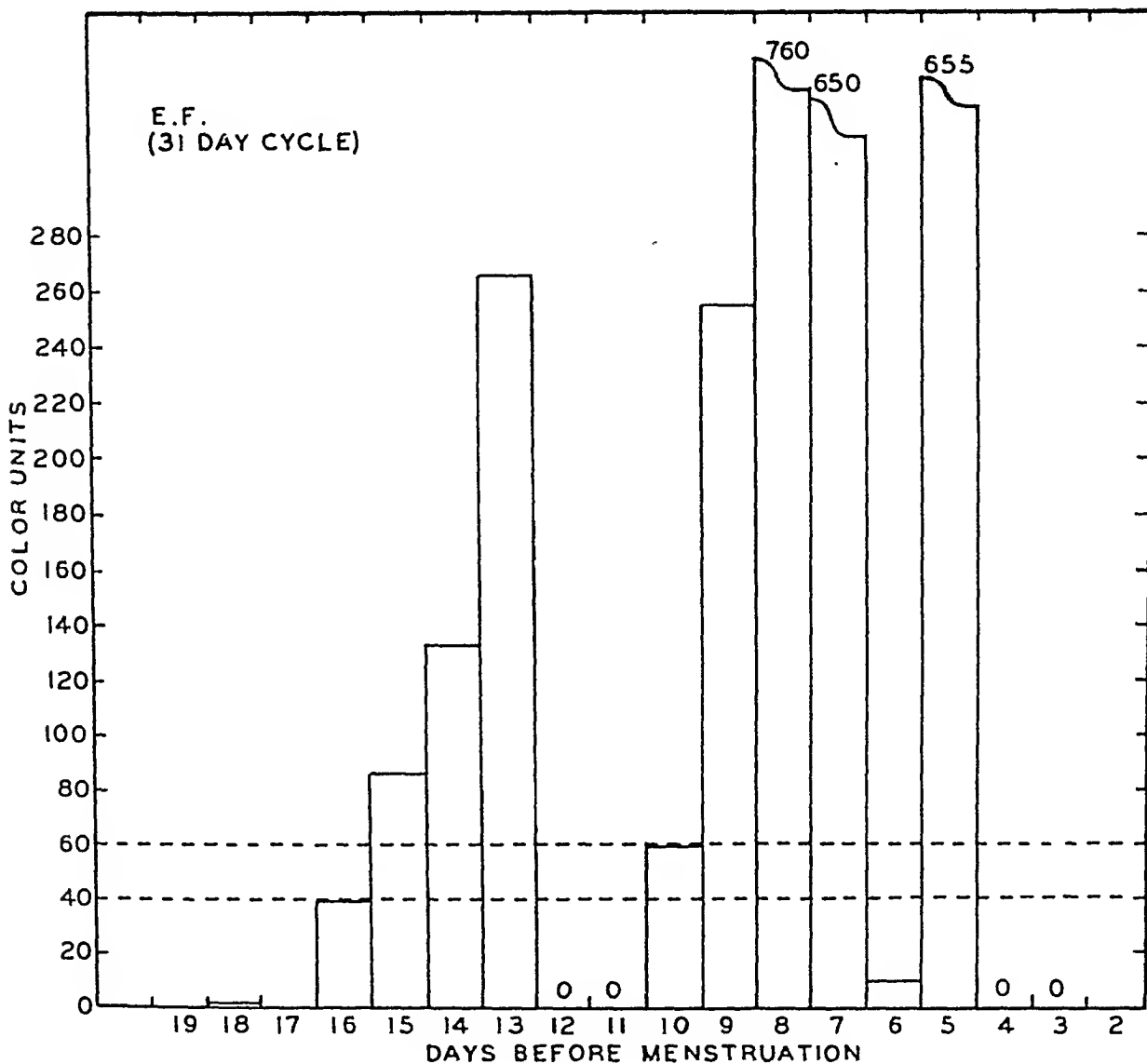


Fig. 2A.

As seen in the graph, there is considerable variation in the color resulting from the addition of identical amounts of sodium pregnanediol glucuronide. This occurs in spite of quantitative methods, and the variable recovery is unexplained.

Results

1. *Nonpregnant Women.*—Urine specimens were collected from five apparently normal women during the latter half of the menstrual cycle. Follow-up studies confirmed that none was pregnant. Collections were begun ten to seventeen days before the expected date of bleeding. In one case, only three specimens were collected, but in four women complete collections during the luteal phase were obtained. The results of the determinations are shown in Fig. 2.

It is seen that in the cases graphed there are 18 values recorded which fall within the range regarded as positive. In the fifth case, which is not graphed, the values for the three specimens collected eleven, nine, and seven days before bleeding were 34, 24, and 310 C.U., respectively. The last was a strongly positive test.

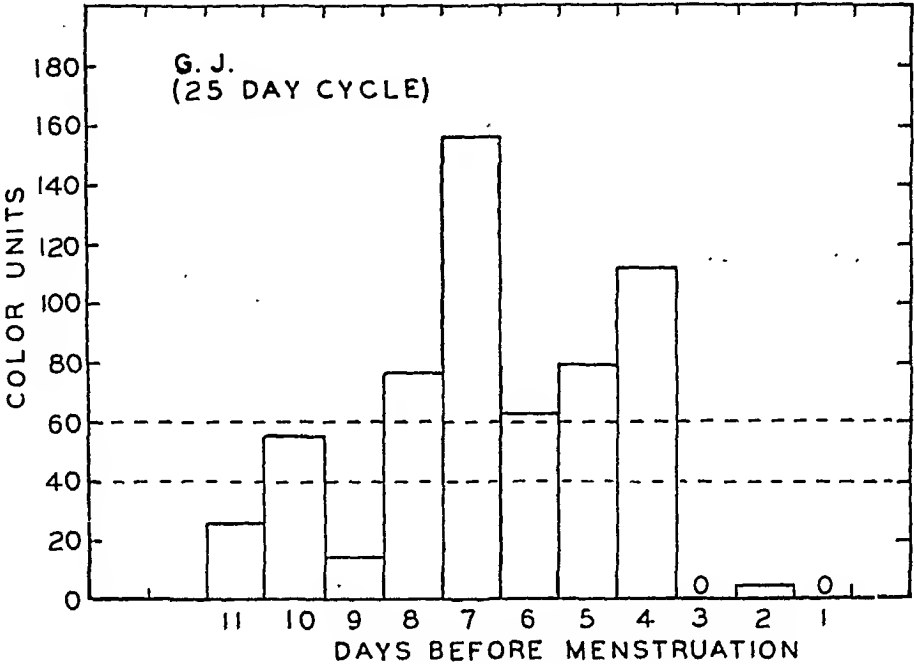


Fig. 2B.

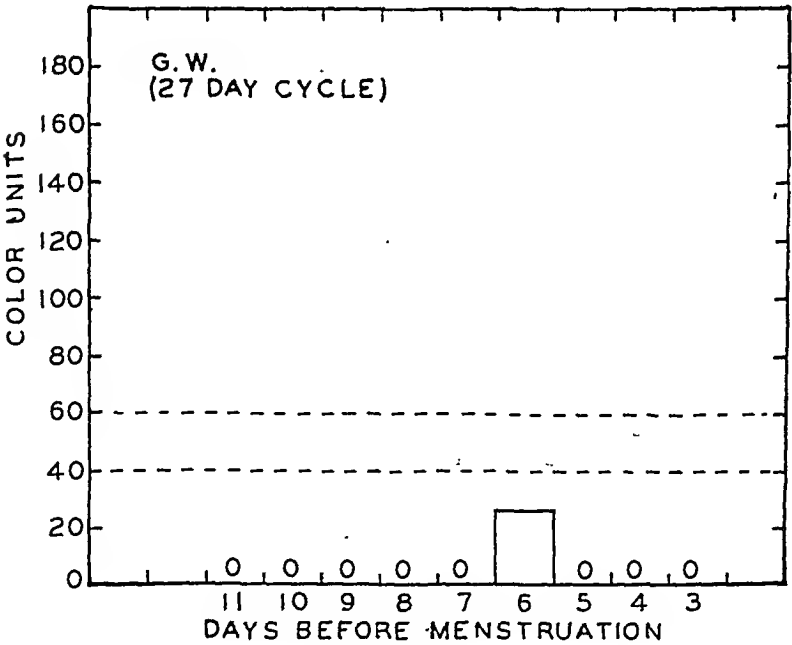


Fig. 2C.

2. Early Pregnancies.—

CASE 1.—M. J. complained of abdominal pain. A history was obtained of amenorrhea for six weeks, followed by vaginal spotting. The abdomen was diffusely tender and a mass was palpable in the right adnexal region. The impression, confirmed by subsequent follow-

up, was a six to seven weeks' intrauterine pregnancy and hydrosalpinx. The color test gave a positive reading of 520 color units.

CASE 2.—C. D. was being followed because of previous abortions. The test was run at the seventy-fourth day of the pregnancy and gave a negative reading of 22 color units. The gravimetric pregnanediol determination at this time was 3.2 mg./24 hours. This pregnancy has been followed to six months and is progressing normally.

CASE 3.—E. G. also was being followed because of previous abortions. A test was run at eight weeks of gestation, and the reading was positive at 163 color units. The pregnancy has been followed to six months and is apparently normal.

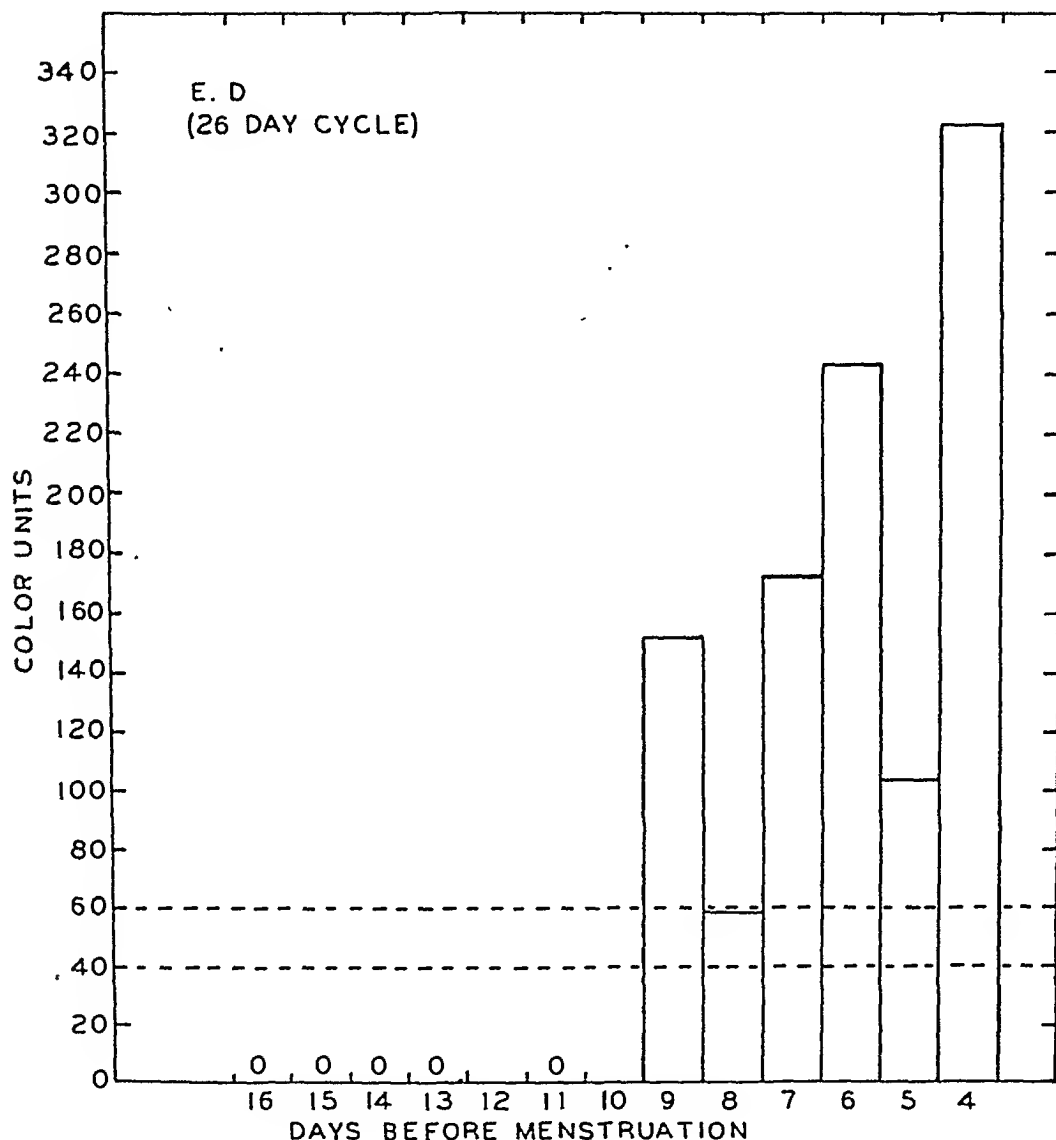


Fig. 2D.

3. Conditions Simulating Pregnancy.—

CASE 4.—R. B. was admitted complaining of amenorrhea of six months' duration, previous menstrual irregularities, and a questionable increase in the amount of hair on her arms and legs. A pelvic examination revealed a mass in the right adnexal region 5 to 6 cm. in diameter. At laparotomy a right ovarian tumor was removed, which proved to be an arrhenoblastoma. The color test before operation was 510 C.U., and after operation showed no pregnanediol. The 17-ketosteroid determination done before operation gave a value of 59 mg./24 hours; after operation this fell to 11 mg./24 hours.

CASE 5.—P. H. was registered in the obstetric dispensary with the clinical diagnosis of "an unquestionable 10-week pregnancy." She was admitted for termination of the pregnancy because of adenocarcinoma of the breast with metastases. A curettage revealed metastatic adenocarcinoma and normal interval endometrium with no evidence of pregnancy. The color test gave a positive reading of 340 color units.

CASE 6.—C. B. was admitted complaining of cramping abdominal pain and frequent vaginal bleeding of two months' duration. A laparotomy revealed a corpus luteum cyst with recent hemorrhage and pelvic inflammatory disease. The color test gave a reading of 0 color unit.

CASE 7.—M. R. was admitted on the obstetric service because of cessation of fetal movements for six weeks. The last menstrual period had been fifty-seven weeks previous. Operation revealed an abdominal pregnancy with a macerated fetus. A specimen collected at the time of operation showed 720 color units.

CASE 8.—M. C. was admitted complaining of sudden pain in the left lower quadrant, irregular bleeding, and amenorrhea for five weeks. The clinical diagnosis was ectopic pregnancy. An operation showed salpingitis with torsion and infarction of the tube. The color test gave a reading of 173 color units.

Rat pregnancy tests done on all patients in this group were consistently negative.

4. *Male Urines*.—Six specimens of male urine were examined. All showed 0 color unit.

Discussion

Forty-nine specimens from five normal nonpregnant women were tested by the Guterman method; 19 positive and 2 doubtful tests were obtained. These results show that false positive tests for pregnancy are obtained frequently during the luteal phase in nonpregnant women. The importance of this observation is that *in cycles prolonged by late ovulation the corpus luteum may be at the peak of functional activity at a time when the bleeding period is considered to have been missed*. Furthermore, the colorimetric values recorded in early pregnancy overlap those of normal cycles (see Cases 1, 2, and 3, and Fig. 2). This is confirmed by the gravimetric studies of several workers. Venning and Browne¹⁰ report values up to 8.1 mg./24 hours, Hain and Robertson⁶ 14 mg./24 hours, and Tien¹⁸ 13.3 mg./24 hours in normal nonpregnant women, while the latter gives values as low as 6.2 mg. of pregnanediol per 24 hours in the first month of normal pregnancies.

In the three cases of early pregnancy studied, two showed positive tests in the seventh or eighth weeks. One case gave a negative test in the seventh week, but this patient was known to be an habitual aborter. Gravimetric determinations of the pregnanediol excretion in this laboratory gave a value of 3.2 mg./24 hours at the time of our test. This pregnancy, however, has been maintained for six months without hormone therapy and is apparently normal. Thus it appears that the Guterman test, usually positive in early pregnancy, may occasionally be negative in pregnancies which continue normally.

Guterman maintains that a positive test in the presence of amenorrhea indicates a normal pregnancy. There are several conditions in which this assumption is not valid. The case of arrhenoblastoma (Case 4) shows that a high level of 17-ketosteroid excretion gives a positive test.¹ These compounds give a positive color reaction according to Kober.¹⁵ Case 5 is an excellent example of a

positive test in the presence of amenorrhea and uterine enlargement due in this instance to carcinoma metastases. Case 8 was diagnosed clinically as ectopic pregnancy and a positive Guterman test obtained. Operation showed salpingitis with torsion and infarction of the tube. The rat pregnancy test was negative in all three of these cases.

Case 6 is a case of corpus luteum cyst giving a negative test. This may have been due to the hemorrhage present.

Summary

1. The Guterman test for pregnancy was found positive in a large percentage of normal nonpregnant women during the luteal phase of the menstrual cycle.

2. In one case of an apparently normal pregnancy of seven weeks' duration, a negative Guterman test was obtained.

3. A positive Guterman test may be obtained when large amounts of 17-ketosteroids are present in the urine, as in arrhenoblastoma.

4. In the presence of amenorrhea the Guterman test may be positive on the basis of a functioning corpus luteum without pregnancy.

The authors wish to thank Dr. G. E. Seegar Jones and Dr. Eleanor Delfs for their able advice and assistance in this work, and Mr. H. M. Stran for his help in the laboratory.

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UTERUS DIDELPHYS AND ITS CLINICAL SIGNIFICANCE IN PREGNANCY

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THE degree of duplicity of the uterus, cervix, and vagina depends entirely upon the degree of failure of fusion of the Müllerian ducts. When there is a complete lack of fusion, double uterus, double cervix, and double vagina result. This type of abnormality is called "complete uterus didelphys." The degree of lack of fusion of the Müllerian ducts determines the type of abnormality that will result, and any number of different types of partial or complete duplication of the uterus, cervix, and vagina is possible. The lack of fusion may be complete so far as the uterus is concerned, while the cervix and vagina may be completely fused. No type of duplication of these organs except the one resulting from complete lack of fusion of the Müllerian ducts will be discussed in this paper. Although this complete lack of fusion is the rarest of the pelvic malformations, it is probably true that the incidence of congenital anomalies in the female genitalia is higher than statistics would indicate. Many women probably go through life without knowledge of the defect. The literature on this abnormality is extensive but most authors have included in their reports all types of pelvic and uterine abnormalities. For this reason only one type of malformation will be discussed in this report.

There are four times during a woman's life when this abnormality is most likely to be found. First, during adolescence, especially if the patient complains of some menstrual disturbance or dysmenorrhea; second, at the time of premarital examination; third, after marriage, should the patient complain of dyspareunia or unexplained abortion; and fourth, during pregnancy. In this paper we are concerned primarily with the latter group because uterus didelphys is usually of no clinical significance except in pregnancy. The abnormality may, however, be complicated by any type of pelvic disease, in which case the patient's complaints will usually be referable to the disease and not to the pelvic anomaly.

The history in these cases is usually of little value. The individual may complain of some menstrual disturbance, delay in onset of the flow, intermenstrual bleeding, dysmenorrhea, dyspareunia, or even amenorrhea. All of the cases reported gave a history of one or more of these symptoms.

The primary diagnosis may in some cases be difficult. The presence of a mass in the pelvis may be difficult to differentiate from a pedunculated fibroid or an ovarian cyst. Hysterosalpingography may be of value. Whenever a vaginal septum is found, whether it be partial or complete, a careful search should be made for a double cervix and double uterus either partial or complete.

The clinical significance of uterus didelphys during pregnancy is important. Many unusual cases have been reported and the methods by which they have been handled have varied considerably. Naturally it is impossible to draw any definite conclusions from a single case and yet this is the error that many authors have made. Some men have treated these cases much the same way as a normal pregnancy and have disregarded the abnormality present, while others have advised extremely radical surgery even in the presence of pregnancy. In November, 1931, Frank R. Smith gave the most complete and intelligent report thus far presented. He stated that this abnormality is found once in about every twenty-seven or twenty-eight thousand women and once in every fifteen hundred pregnancies. Sterility is much more common among these women, but once pregnancy occurs the cases are about even.

Complications During Pregnancy.—Abortion and premature labor seem to be quite common. This tendency, according to many authors, is most common in breech and transverse presentations. Vaginal bleeding of varying amounts is a relatively common symptom and is usually due to bleeding from the nonpregnant uterus. If this blood is examined under the microscope, decidual tissue will be found. This is due to the fact that the reaction of the endometrium of the nonpregnant uterus is the same as in an ectopic pregnancy. Following delivery the decidua in the nonpregnant uterus is cast off. The nonpregnant uterus usually increases two or three times its size. Premature separation of the placenta or abruptio placentae and placenta previa, either partial or complete, have been reported. These complications were present in Cases 2 and 4.

Complications During Labor.—Labor may be prolonged because of weak or deficient musculature. Many authors list a uterus didelphys as one of the causes of uterine inertia. Rupture of the uterus may occur during labor either because of a very thin lower uterine segment or as a result of dystocia. Prolonged labor and weak uterine contractions and dystocia resulting from impaction of the nonpregnant uterus usually result in a high percentage of operative deliveries. Fetal morbidity and mortality are increased as a result of operative interference. Malpositions and abnormal presentations are more common, due to interference from the nonpregnant uterus.

No cases of ruptured uterus were observed in this series. Obstruction of the birth canal by the nonpregnant uterus was seen in Cases 1, 2, and 4. Fetal morbidity as a result of operative interference is illustrated in Case 6. Malposition was seen in Case 4 (two pregnancies).

Postpartum Complications.—Postpartum hemorrhage and subinvolution are listed as common postpartum complications probably due to poor contraction of the uterine musculature. Retained placenta probably results from malposition of the placenta and interference with normal uterine contractions by the nonpregnant uterus or from weak or deficient uterine contractions of the pregnant uterus. None of these complications occurred in any of the cases reported in this paper.

No fixed rule or type of operation can be applied in the treatment of this abnormality when pregnancy occurs. Each case is an individual problem and to apply a general rule to all such cases would be rendering the patient a grave injustice. To be sure, all of these patients should be under the care of a competent obstetrician. Prenatal care should include close observation, frequent rest in bed if necessary, abdominal support when indicated, and careful avoidance of trauma of any kind. Should premature separation of the placenta or premature labor occur, one should be prepared, if necessary, to do an abdominal section. If a test of labor is decided upon, one should be prepared to do a cesarean section if dystocia or fetal embarrassment should occur. Cesarean section will eliminate maternal exhaustion, prolonged labor, undue complications, and decrease fetal and maternal mortality and morbidity.

Unless the deformity is very slight and the nonpregnant uterus very small, dystocia is more likely to occur. The nonpregnant uterus may become incarcerated in the hollow of the sacrum or in other ways block the maternal pelvic outlet. If a suspension of both uteri has been previously done and the patient then becomes pregnant, uncomplicated labor and delivery may result. This probably is due to the fact that the nonpregnant uterus is carried up out of the pelvis, and when labor occurs it fails to cause any dystocia. Such a case was reported by Browne in 1938 and a similar case is reported in this paper (Case 3).

As mentioned above, no special treatment of these cases, outside of pregnancy, is necessary unless the patient complains of dyspareunia or the abnormality is associated with some pelvic disease or tumor. Dyspareunia is usually caused by the vaginal septum and the removal of the septum is usually sufficient in these cases.

The indications for cesarean section are weakened musculature, dystocia, abruptio placentae, premature separation of the placenta, and placenta previa. It is advisable to have all of the patient's pelvic measurements substantiated by x-ray pelvimetry. All cases of contracted pelvis and borderline contractions should be treated by cesarean section. A patient with a very large outlet probably should be permitted a test of labor, but the obstetrician should be prepared to do an abdominal section if necessary. If during the latter month of pregnancy the nonpregnant uterus can be palpated and proved to be causing any blockage of the pelvic canal, elective cesarean section should be done. In the presence of uterus didelphys, we believe it is more conservative to do an elective cesarean section than to submit the patient to unnecessary risks. A competent obstetrician should, however, know when to operate and when not to operate.

CASE 1.—P. L., aged 22 years, was first seen July 12, 1944. Last menstrual period, Jan. 25, 1944. Calculated date of confinement, Nov. 2, 1944.

Catamenia: Began at the age of 13 years, never regular. Usually menstruates every three to six weeks. Has occasionally had periods of amenorrhea lasting from two to six months. Menses usually last about five days, with dysmenorrhea severe.

Operations: Vaginal septum removed Feb. 28, 1943, because of dyspareunia. The condition of uterus didelphys was not discovered until the time of this examination.

Blood count: Normal.

Weight: Normally 98 to 103 pounds.

Serology: Negative.

Pelvimetry: Within normal limits.

Pelvic examination: Two cervixes. The uterus on the right side is more fully developed. The pregnancy is in the right uterus with a smaller mass felt in the left lower quadrant.

On Nov. 20, 1944, examination revealed the presenting part (head) was not engaged. An obstructing mass (left uterus) could be felt in the pelvis.

Treatment: The patient was delivered by classical cesarean section. The pregnancy was in the right uterus and the obstructing mass was the nonpregnant left uterus. The peritoneal reflection of the urinary bladder was attached anteriorly to both uteri and then dipped down between the two uteri to become attached to the peritoneum in the pouch of Douglas. Each uterus had one tube and one ovary. The mother had an uncomplicated convalescence and the baby is living and well.

CASE 2.—M. G., aged 24 years, was first seen Sept. 11, 1944. Last menstrual period, June 27, 1944. Spotting occurred July 23, 24, 26, 27, and 28, 1944. Calculated date of confinement, April 3, 1945. Although the patient had been married for three years, the condition of uterus didelphys was not discovered until the time of this examination. No history of dyspareunia.

Catamenia: Began at the age of 12 years. Twenty-eight day type, lasting three to four days. No menstrual irregularities.

Operations: Appendectomy and operation for intussusception at the age of eight months.

Blood count: normal. Prothrombin: 106 per cent of normal. Rh factor: positive. Serology: negative. Pelvimetry: within normal limits.

Examination revealed a double uterus, double cervix, and double vagina. The left uterus was considerably larger than the right. The left vagina was considerably larger than the right.

Oct. 4, 1944, the patient was admitted to the hospital because of slight vaginal bleeding. It was definitely determined that the bleeding was coming from the right nonpregnant uterus. Microscopic examination of this blood revealed the presence of decidua tissue. Bed rest was continued until October 18 when the patient was permitted to leave the hospital. Her activities at home were considerably restricted. There was very slight vaginal bleeding on October 31.

Feb. 10, 1945, the patient had slight vaginal bleeding definitely coming from the right uterus.

March 10, 1945, the patient was admitted to the hospital with severe painless vaginal bleeding. The abdomen was soft and there was no pain on palpation. The uterus was not contracted. The bleeding was from the left uterus. Rectal examination revealed dilatation of the left cervix amounting to about 3 cm. An obstructing mass could be felt in the right pelvis. It was felt that the patient had a placenta previa and she was immediately prepared for a cesarean section.

The patient was delivered by classical cesarean section. The pregnancy was in the left uterus. The placenta was of the marginal type and was attached anteriorly. The peritoneal reflection of the urinary bladder was attached anteriorly to both uteri and then dipped down between the two uteri to become attached to the peritoneum in the pouch of Douglas. Each uterus had one ovary and one tube.

The patient made an uncomplicated postoperative convalescence. The baby was normal and required no special treatment.

CASE 3.—G. D., aged 21 years, was first seen on June 1, 1942, with a chief complaint of pain in the right lower quadrant.

Catamenia: Began at the age of 12 years. Twenty-eight- to thirty-day type, lasting five to six days. Occasional spotting between periods.

Abdominal examination revealed local tenderness over McBurney's point. Vaginal examination revealed a double vagina, the one on the left being somewhat larger than the right. There were two separate cervices, the one on the left being somewhat larger. Two separate masses were palpable in the cul-de-sac and these were thought to be two separate uteri. The patient had no previous knowledge of this condition.

On June 11, 1942, a laparotomy was done for appendicitis. Examination of the pelvic contents revealed the uterus on the left side to be somewhat larger than the one on the right. Each uterus had one tube and one ovary. The urinary bladder was attached anteriorly to both uteri and then dipped down between the two uteri and was attached to the peritoneum in the pouch of Douglas. Both uteri were markedly retroverted. The uteri were lifted out of the cul-de-sac and the round ligaments were shortened by a modified Gilliam technique, using black silk. The patient made an uneventful postoperative convalescence. The patient was advised to obtain competent obstetric consultation should she become pregnant.

The patient became pregnant in November, 1943. She had moved from Michigan and was delivered in another state, Aug. 7, 1944. A letter from the attending obstetrician stated that the pregnancy was in the left uterus, and the patient had a perfectly normal prenatal period. She had no pain or discomfort and there was no bleeding. Her labor was progressive and without complications of any kind. There were no postpartum complications. The infant was normal and is living and well.

CASE 4.—S. H., aged 19 years, was first seen May 16, 1940, with a chief complaint of miscarriage. Last menstrual period was Jan. 10, 1940. On April 22, 1940, the patient began to bleed vaginally and on April 26 apparently passed the fetus and membranes intact. She stated that she flowed heavily for three days and then had slight bleeding for an additional two weeks.

Catamenia: Began at the age of 12 years. Twenty-eight- to thirty-two-day type, lasting four days. Occasional spotting between periods.

Examination showed a double vagina, the one on the left side being the larger of the two. There were two cervices and two separate uteri. The pregnancy was apparently on the left side because a small laceration of this cervix could be demonstrated. The patient was again seen July 8, 1940. Her last menstrual period was May 22 to 28, 1940. No history of dyspareunia. Examination at this time revealed the pregnancy to be in the left uterus. Pelvic measurements revealed a justo minor pelvis with some flattening. The patient was seen on September 7 complaining of vaginal bleeding and this continued until September 17. This bleeding was definitely from the right uterus. A urine pregnancy test at this time was positive. X-ray of the abdomen taken Jan. 23, 1941, showed a single pregnancy with the fetus in dorsolumbar transverse presentation with the fetal skull in the left flank.

On Feb. 17, 1941, a classical cesarean section was done. The pregnancy was in the left uterus, the fetus was in the position as described in the x-ray, and the right uterus was wedged in the pelvis. The placenta was attached to the posterior wall of the uterus. The mother made an uneventful postoperative convalescence. Baby is living and well.

A second cesarean section was done Jan. 13, 1943. The pregnancy at this time was in the right uterus and the fetus was in the sacrum right posterior breach presentation. The patient again made an uneventful postoperative convalescence.

As in previous cases described, each uterus had one tube and one ovary. The bladder was attached anteriorly to both uteri and then dipped down between the two uteri to become attached to the peritoneum in the pouch of Douglas. The mother made a normal convalescence. Baby is living and well.

During the past six months, the patient has complained of dyspareunia. The vaginal septum is to be removed in the near future.

CASE 5.—M. L., aged 26 years, was first seen, March 24, 1945, with chief complaint of a missed menstrual period. Last menstrual period, Feb. 15 to 21, 1945. The patient gave a history of exposure and no history of dyspareunia.

Catamenia: Began at the age of 12 years. Thirty-day type, six to seven days' duration. Occasionally misses a month.

Examination revealed double vagina and double cervix. Both cervices were small, although the cervix on the left side was somewhat larger. Two uteri were palpable. The one on the left was somewhat larger.

A urine pregnancy test was done and this was negative. The patient began to menstruate April 26 and the period was of six days' duration.

Because the patient had no complaints, she was advised to do nothing about the pelvic abnormality. She was advised to obtain competent obstetric care should she become pregnant.

CASE 6.—E. H., aged 30 years, came in for pelvic examination on April 30, 1938. The following history was obtained from both the patient and the hospital at which she had been operated upon.

She was admitted to the hospital June 28, 1928, with a chief complaint of dyspareunia. A vaginal septum and two cervices were found and a hysterosalpingography revealed a double uterus. On July 5, 1928, the following operation was done: section of the vaginal septum, inflation of the tubes from within outward, and an appendectomy. The septum was comparatively thick and examination of the pelvic structures revealed complete uterus didelphys, each uterus having one tube and one ovary. The uteri were about equal in size although slightly smaller than normal. There was no retroposition. On April 30, 1930, the patient was delivered vaginally. The delivery was terminated with instruments and resulted in a child with spastic paralysis. The birth injury was directly attributed to the instrumental delivery. The child became a very difficult nursing problem for the family and finally succumbed at the age of 8½ years. To my knowledge there had been no subsequent pregnancies.

Examination on this date, April 30, 1938, revealed the condition as described above. The vaginal septum had been removed and there were two separate cervices of about equal size. Two separate uteri were easily palpable.

Conclusions

1. Uterus didelphys is a pelvic abnormality resulting from complete lack of fusion of the Müllerian ducts.

2. Pregnancy may occur in a woman with uterus didelphys. Some cases have been reported in which pregnancy has occurred simultaneously or at different times in both uteri.

3. No special treatment of uterus didelphys outside of pregnancy is necessary unless the patient complains of dyspareunia or unless the abnormality is associated with pelvic disease or tumor.

4. Careful supervision during the prenatal period is advised. All individuals with uterus didelphys should have careful pelvic measurements including x-ray pelvimetry.

5. During pregnancy-abortion, premature labor, abruptio placentae, and premature separation of the placenta are more common than when uterus didelphys is not present.

6. During labor-maternal exhaustion, fetal embarrassment, prolonged first stage of labor, rupture of the uterus, and dystocia may occur. Oblique and other abnormal presentations are more common.

7. Following labor-postpartum hemorrhage, retained placenta, and subinvolution may occur. None of these complications were observed in this series.

8. Operative deliveries may result in increased fetal morbidity and mortality. This was not true in this series, except in Case 6.

9. Milder forms of uterus didelphys will probably cause no trouble.

10. Elective cesarean section will in certain cases be the operation of choice. Each case must be treated individually, and whenever advisable a test of labor should be given. Uncomplicated delivery will occur in many cases.

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766 FISCHER BUILDING

UTERUS DIDELPHYS

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VARYING degrees of abnormality in the female genital tract are due to nonunion of the Müllerian ducts. The terminology for double uterus is confused (DeLee lists nine variations), but Dorland's *Medical Dictionary*, twentieth edition, defines double uterus or uterus didelphys as "either of two distinct uteri occurring side by side in the same individual."

The gross abnormalities are rare. Taylor¹ found 262 cases of double uterus with pregnancy reported in the literature of recent years. Obenour² found only 15 cases of double uterus and vagina reported in different parts of the world since 1879. All investigators³⁻⁸ emphasize the difficulty of diagnosis, even after one or more pregnancies. Findley⁹ suggested that such cases are usually fertile, although abortions and premature deliveries are more frequent. He notes Robertson's case of a woman who had had 13 babies in five pregnancies. Ladd and Chisholm¹⁰ report successful surgery for incontinence in a 12-year-old girl with double uterus, vagina, and rectum. Early diagnosis is important because of the dangers of subsequent pregnancy.

Case Report

F. L., a 38-year-old nullipara, entered Immanuel Hospital, May 1, 1945, complaining of severe disabling pain in the lower right abdominal quadrant during her menses, requiring opiates for relief from excruciating pain, particularly since an operation five years ago. At that time a laparotomy (in another city) revealed a double uterus in a retroflexed position and a double vagina. The vaginal septum was removed; a Baldy-Webster type of uterine suspension and appendectomy were also done. She consulted the author six months after her marriage, upon advice of her local physician, who had suggested ligation of the Fallopian tubes to prevent conception. General physical examination was essentially negative.

Pelvic examination showed a cervix of about normal size containing two openings with a small sulcus between. Close scrutiny showed slight scarring from the previous removal of the vaginal septum. Upon bimanual examination, the corpus was slightly larger than normal, in a normal position, but with a rather marked fullness and hardness on the right side. For diagnostic purposes iodized oil was injected into the right cervical os; the oil failed to enter the uterine cavity, but ran out around the cannula and into the vaginal vault. When the cannula was introduced into the left cervical opening, the iodized oil flowed freely into the endometrial cavity and out into the Fallopian tubes, as shown by the roentgenogram (Fig. 1).

A laparotomy was done May 2, 1945, under morphine-scopolamine analgesia and general ether anesthesia. The peritoneal cavity was entered after removal of the old midline scar. Numerous coils of both small and large intestine were found to be firmly adherent to the posterior surface of the uterus, extending from the fundus down into the posterior cul-de-sac. Adherent bowel was also found to obliterate the right adnexal region from view. Release of these adhesions by both blunt and sharp dissection disclosed the uterus with a cleft dividing the uterine corpus into an apparently normal left-sided and a larger right-sided portion. The entire right side of the uterine corpus seemed to be composed of a solitary fibroid tumor, which approached the size of a large orange at the widest diameter. The uterine corpus was not divided into two distinct bodies, but rather fused, as described above.

The right Fallopian tube was long and kinked in several places; a cystic ovary the size of an English walnut was found buried in a mass of adhesions in the right adnexal region and was punctured by use of a hemostat. The left tube, buried by more or less soft adhesions, and a small ovary were found near the base of the broad ligament.

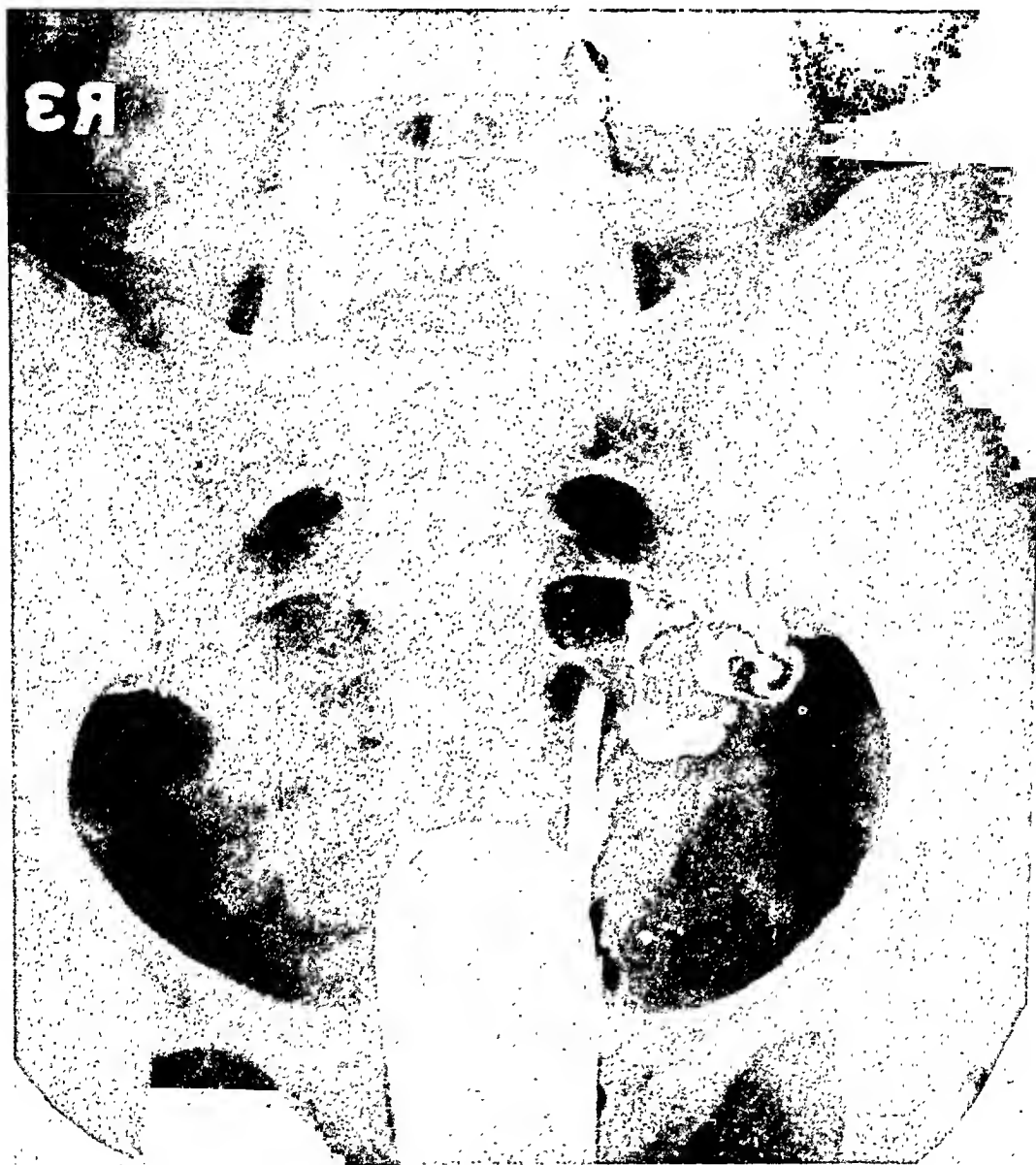


Fig. 1.—View showing iodized oil extending out into entire portion of left Fallopian tube and slight amount into peritoneal cavity.

A subtotal hysterectomy was done with some difficulty because of a severe, clockwise torsion of the uterus; it was feared that total hysterectomy would damage the ureter, which was obliterated by dense adhesions of bladder to uterus. Upon opening the uterus after hysterectomy, the right endometrial cavity was found to be completely obliterated by a fibroid tumor filling the entire right side of the uterine corpus. The left side contained a very narrow endometrial cavity (Fig. 2).

Recovery was uneventful and the patient was dismissed on the tenth postoperative day.



Fig. 2.—Anterior view of uterus reconstructed after specimen was removed from abdomen showing a probe in right cervical canal and showing right endometrial cavity being blocked by a large fibroid. Left portion of uterus was quite normal in appearance. Both sides of the uterus were opened by incision down to endometrial cavity previous to making above sketch.

Summary

This case report is presented to add another case of uterus didelphys to the literature. It also differs from many others in that this patient was seen late in the childbearing age, although only a few months after marriage. Her primary complaint was disabling dysmenorrhea, a condition easily conceivable in view of her pelvic pathology. This has been entirely corrected since performance of pelvic surgery.

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EVALUATION OF A NEW CONTRAST MEDIUM FOR HYSTEOSALPINGOGRAPHY*

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THE well-known shortcomings of the various contrast media that have been available for the x-ray study of the uterus and the uterine tubes have caused gynecologists generally to restrict the use of this valuable diagnostic procedure. This attitude has been shared by the Department of Gynecology of the Jefferson Medical College Hospital where, until recently, hysterosalpingography has been used only occasionally. However, the development of the medium herein described has convinced us that this procedure now can be used freely under the proper circumstances without fear of injury to the pelvic tissues.

During the past twenty-five years, a number of investigators have attempted to develop an ideal contrast medium which, as stated by Neustaedter and his associates in 1933, and restated by Rubin in 1936, should possess the following prerequisites: (1) adequate radiopacity, (2) rapid absorption, (3) freedom from chemical irritation, and (4) proper viscosity.

The first substance to adequately fulfill these requirements was presented by Rubin in 1941. This product, which was akin to the radiographic crystalline iodine compounds employed in urology, consists of a solution (70 per cent) of rayopake (diethanolamine salt of 2, 4-dioxo-3-iodo-6 methyl tetrahydropyridine acetic acid) with 3½ per cent concentration of polyvinyl alcohol which produces the viscosity.†

The toxicology was thoroughly studied in dogs. Based on comparative weights, it was estimated that the average amount (10 to 15 c.c.) administered clinically contains one-fiftieth of the maximum tolerated dose of contrast acid and one five-hundredth of the tolerated dose of polyvinyl alcohol.

In his original communication, Rubin reported the use of Visco-Rayopake in 81 patients with eminently satisfactory results. The radiopacity was equal to that of the iodized oils, the contrast material remained in the tubes long enough to permit radiograms to be made, yet it was almost completely absorbed at the end of thirty minutes with very little clinical evidence of local chemical irritation. One patient, in whom the procedure was carried out in the presence of unfavorable clinical conditions, experienced a febrile reaction, but recovered without serious damage to the tubes.

*Presented at a meeting of The Obstetrical Society of Philadelphia, May 3, 1945.

†It was developed according to specifications by Hoffman-LaRoche, Inc., and was called *Visco-Rayopake*.

Since the publication of Rubin's paper, Goldberger has reported the use of Visco-Rayopake in 72 patients, Bernstein in 52 patients, and Norment in 20 patients. Each of these authors shared Rubin's enthusiasm for this new contrast medium.

We have had the opportunity of using Visco-Rayopake in 71 patients. During our early experience, we limited its use to patients whose tubes were closed by previous sterilization operations. Later we extended its use to patients in whom the Rubin test had previously indicated tubal obstruction and, finally, we used it in a small group of patients about whose tubes we had no preliminary information.

All of the patients were hospitalized for part of a day, and each was given $1\frac{1}{2}$ grains of seconal or 3 grains of sodium amytal and $\frac{1}{150}$ grains of atropine sulphate hypodermically about one-half hour before the salpingography was done. Following the procedure, they were confined to bed for three or four hours and then permitted to leave the hospital.

The usual clinical contraindications to uterotubal insufflation were carefully observed, although the test was carried out in the latter half of the menstrual cycle in some of the patients who had been sterilized previously by tubal ligation. Careful aseptic technique was observed in all cases. The cannula was inserted into the cervical canal after the usual vaginal preparation in the operating room, and the patient then transferred to the x-ray department. Under fluoroscopic control, the Visco-Rayopake was carefully injected with a 20 c.c. Luer Lok syringe. This enabled us to observe the freedom with which the fluid medium passed from the endometrial cavity into the tubes, as well as to determine the most favorable time for making the x-ray exposure. In some instances, the opaque material did not enter the tubes until slightly increased pressure was maintained on the plunger of the syringe for a brief period of time, although usually when the uterine tubes were patent it flowed freely without this temporary delay.

As a rule, 3 or 4 c.c. were required to fill the uterine cavity, when the tubes were patent, 10 to 15 c.c. were injected. Stereoscopic films were made in the anteroposterior position at the optimum time as indicated by fluoroscopic observation. In our early experience, we routinely made a flat film one hour later. This invariably failed to show any evidence of the opaque medium, indicating that it had been absorbed. Films made routinely one-half hour after the injection revealed only very slight amounts of the medium remaining in the pelvis, and in many cases it had disappeared completely. This rapid absorption of the Visco-Rayopake from the peritoneal cavity constitutes its most outstanding advantage.

The density of the shadows cast by the Visco-Rayopake was highly satisfactory under the fluoroscope and also on the x-ray films. The excellent visualization of the tubes was made possible, of course, by the high viscosity of this fluid medium which causes it to remain in the tubal lumen long enough to permit x-ray films to be made.

The local discomfort produced by injecting Visco-Rayopake into the uterus and uterine tubes was not marked. In some instances, sharp menstrual-like cramps resulted when the uterine cavity was overdistended by too rapid injection. This was relieved immediately by the withdrawal of a small amount of the fluid. Although an accurate notation of the local pain reaction was not made at the time each patient was studied, it is our impression that most of the patients were aware of some mild discomfort when the contrast medium flowed into the peritoneal cavity. This varied in intensity with the individual patient and usually disappeared within one hour. A few patients stated that it persisted for a longer time. One patient required medication for relief of pain. All of the patients left the hospital within three or four hours. All were examined subsequently and none showed any evidence of local inflammatory reaction.

Two of the patients, whose tubes were closed, were operated upon later. One was found to have bilateral tuberculous salpingitis, but there was no evidence that the injection of the contrast medium had activated the inflammatory process which was quiescent. In the second patient, one tube was resected and transplanted into the uterus. Subsequent salpingography showed this tube to be freely patent.

Of the 79 patients examined by us, the uterine tubes were closed in 54. Twenty-four of these had been sterilized by tubal ligation. In the remaining 30 patients, the tubes were closed at the uterine ends in 8, and at the fimbriated ends in 16, while in 6 one tube was closed at the uterine and one at the fimbriated ends. In 25 patients, the contrast medium passed freely into the peritoneal cavity. One tube was patent in 6, and both tubes were patent in 19.

Preliminary Rubin tests were done in 37 patients. Complete closure was indicated in 27, but in 10 of these uterosalpingography proved both tubes to be freely patent, and in 4 others one tube was patent. In 3 instances in which high pressures during the insufflation test indicated partially occluded tubes, the Visco-Rayopake passed through freely.

It is our impression that uterosalpingography has been regarded generally as a more accurate test of tubal patency than the carbon dioxide insufflation test. However, it has not been used as a routine procedure in some clinics because of the shortcomings of the available media and especially because of the danger of local tissue damage by the commonly used iodized oils, which remain in the tissues for an indefinite period of time. We believe that Visco-Rayopake, as presented by Rubin in 1941, has overcome this difficulty. With such a medium available, gynecologists need have no hesitancy in carrying out hysterosalpingography in all patients in whom nterotubal insufflation indicates obstruction.

Summary

Visco-Rayopake (diethanolamine salt of 2, 4-dioxo-3-iodo-6 methyl tetrahydropyridine acetic acid) a new opaque medium, which was introduced by Rubin in 1941 has been found to be highly satisfactory for x-ray study of the uterine tubes. The outstanding advantage of this substance is due to the fact that it is well tolerated by the tissues and is rapidly absorbed from the peritoneal cavity.

It was used to study the patency of the uterine tubes in 79 patients. In 25 of these, the Visco-Rayopake flowed freely into the peritoneal cavity where it was absorbed within thirty minutes.

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1930 CHESTNUT STREET

THE COMBINED MANCHESTER-WATKINS INTERPOSITION OPERATION IN THE TREATMENT OF PROLAPSE OF THE UTERUS*

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AFTER using various types of operations for prolapse of the uterus in this Service, preference is now given to the Manchester type for the first- and second-degree varieties, and vaginal hysterectomy for third-degree prolapse cases. The Watkins interposition operation alone is used only for large cystoceles without prolapse of the uterus, for when this operation is done for prolapse of the uterus, recurrence of the prolapse may occur. It is disappointing to do a Watkins interposition operation and get a good result with a cystocele but have the cervix down to the vaginal orifice later. As Phaneuf¹ and others have pointed out, this is more likely to happen if the uterus is atrophied. It is equally disappointing to obtain a good result in the treatment of prolapse of the uterus with the Manchester operation and later have recurrence of the cystocele. My greatest difficulty with the Manchester operation has been in the cases where the cystocele predominates. In marked cystocele, as in any hernia, the fascia is usually so thinned that it is difficult to get sufficient support for the bladder, particularly in the atrophy of old age. To overcome these difficulties, a combination of the Manchester operation with the Watkins interposition procedure has been used in treating first- or second-degree prolapse when accompanied by a very large cystocele.

Technique

The Manchester operation is carried out in the usual way with or without amputation of the cervix depending on its condition and the amount of elongation present. However, amputation is done in the great majority of the cases. The sutures in the stumps of the divided cardinal ligaments are placed, but not tied. The anterior cul-de-sac is then opened and the uterine fundus brought out and interposed, as in the Watkins procedure. All sutures are then tied and the operation completed by doing a high posterior colporrhaphy to narrow the vagina and to care for a high rectocele. This is followed by a perineorrhaphy. The tissues surrounding the vagina, particularly in the upper half, contribute much to the support of the uterus, as shown by Mengert.² In prolapse after hysterectomy this fact is applied, for either incomplete or complete obliteration of the vagina by the Le Fort operation or total colpectomy is utilized in effecting a cure. As the vagina is enlarged in all prolapse cases, narrowing of the vagina by high posterior colporrhaphy and perineorrhaphy is a valuable procedure in any prolapse operation. The extent of the operative narrowing of the vagina depends upon the marital status of the patient. If there is urethrocele or relaxation around the neck of the bladder with stress incontinence, either the Kelly plication or the Kennedy operations are done preliminary to interposition of the uterus. The interposition operation should not be done in women in the childbearing period unless the patient is sterilized.

My first combined Manchester-Watkins interposition operation was done in 1939. In Richardson's³ composite operation the interposition principle is used,

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for the cervix and fundus uteri are removed except a disk of cervix at the internal os which is interposed between the bladder and the vaginal fascia and mucosa. In 1939, Schumann⁴ referred to the combination of the Manchester and Watkins operations. In Crossen and Crossen's *Operative Gynecology*,⁵ the combined procedure is also advocated. No doubt many others use this principle, but I am calling attention again to its value in the operative treatment of prolapsus uteri when the cystocele is marked and the tissues are thinned.

Results

There were 230 patients operated on for prolapse of the uterus from 1934 to 1944. There were 15 combined Manchester-Watkins interposition operations in this series, and all of them were done since 1939. The low incidence of this type of operation is due to the fact that it was used only in first- and second-degree prolapse in which the cystocele was particularly large and the tissues atrophied, and when there was doubt as to whether the usual operation would suffice to correct the cystocele permanently.

In a follow-up study, ten of the fifteen patients were contacted. One patient, a woman 72 years of age with cardiovascular disease, withstood the operation well but died at home of coronary thrombosis three weeks after leaving the hospital. Eight patients reported themselves as well, and the one patient listed as improved complained only of backache, leucorrhea, and dizziness. The anatomic results were good in all of them and, although the cystocele predominated before operation, there was no recurrence of cystocele or prolapse. The results have been very satisfactory in our small experience with the combined Manchester-Watkins interposition operation and it has helped to solve the problem of the large cystocele and prolapse of the uterus better than either operation alone. It has not been used in third-degree prolapse.

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NEONATAL THROMBOCYTOPENIC PURPURA

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PURPURA was first described by Paul Gottlieb Werlhof in 1735 and was known as "Werlhof's disease." However, it was not until 1887 that Denys, a Belgian histologist, pointed out the almost complete absence of platelets from the blood of certain patients with purpura, and thus separated the thrombocytopenic form of the disease. Dohrn described the first case in the newborn in the same year (1887).

Interest in the disease in the neonatal period was not aroused until 1925, when Rushmore reporting on purpura in pregnant women detailed six cases from the literature. The neonatal cases were merely "riders" to the maternal reports. Since then, ten additional cases have been recorded. The rarity of the disease prompted this report.

Case Report

Mrs. G. C., Hospital No. 41-14962, aged 34 years, height 5 feet 1 inch, weight 285 pounds, gravida viii, para v, came to the Outelinie on March 21, 1944, complaining of a "tumor in the abdomen," which was proved to be a "near-term pregnancy."

Elective induction of labor was begun the following evening with 100 mg. stilbestrol orally, and the next morning 1 ounce of castor oil and a soapsuds enema were given. Three hours later the membranes ruptured spontaneously and pains began.

Labor was precipitate (2 hours and 34 minutes) but otherwise uneventful except for difficulty in delivering the large shoulders.

The child, a boy, cried spontaneously but remained dusky. Oxygen, administered for several minutes, failed to clear the cyanosis. Physical examination revealed a normally developed, cyanotic male infant weighing 4,880 grams. The length was 53 cm., the sitting height 38 cm., and the head measurements were within normal limits. The cyanosis cleared considerably in the first twenty-four hours of life.

Thirty-eight hours after birth, the child passed a meconium stool with some blood. Synkamin, 0.5 mg., was given subcutaneously. Three hours later, the baby began to have frequent stools of dark-reddish to black feces that appeared to be meconium mixed with old blood. Later, they were more reddish in color. No blood clots were observed. After repeated plain water enemas, proctoscopic examination revealed no bleeding points.

Blood drawn at this time gave the following values:

Total red blood cells	4,630,000
Total white blood cells	19,050
Differential	
Neutrophiles	74 per cent
Band neutrophiles	10 per cent
Lymphocytes	16 per cent
Bleeding time (Duke's Method)	1½ minutes
Coagulation time (Sabrazé's Method)	5½-6½ minutes
Fragility of the red cells	0.50-0.34 per cent NaCl
Clot retractility	1+
Platelets (average of several counts)	21,000
Hematocrit	51.5 per cent

Reticulocytes	1.3 per cent
Van den Bergh (direct)	11.3
Blood cultures (reported later)	No growth

The Rumpel-Leede arm-band test was questionably positive. Both mother and child were Rh positive. Prothrombin times were as follows:

At 5 hours of age—47 per cent of normal.
At 29 hours of age—38 per cent of normal.
At 53 hours of age (15 hours after vitamin K administration)—97 per cent of normal.

Seven hours after the initial rectal bleeding, a bruised-appearing bluish area, 1.0 cm. in diameter, appeared over the spinous processes from the eleventh thoracic to the last lumbar vertebra. Small petechiae were present about the neck and the upper back.

The rectal bleeding continued for thirteen hours, or until 100 c.c. of citrated whole blood had been given intravenously. Following this, there was no more bleeding from the rectum. A second bruised area, 3.0 cm. in diameter, appeared on the right upper anterior thoracic wall soon after the transfusion.

During the next twenty-four hours, numerous petechiae appeared over the entire body, including the conjunctivae and sclerae.

Four days after the onset, the petechiae and bruised areas began to fade and were practically gone within twenty-four hours. Fracture of the right clavicle was diagnosed, proved by x-ray, and treated with a figure-of-eight halter.

The child was drowsy during his entire hospital stay. On the fifteen day he became more listless, appeared sleepy, and showed slight fever (101.4° F. by axilla) that persisted for seven days. There was no adequate explanation for this febrile course.

Platelet determinations on the mother were always normal. Her postpartum course was uneventful. No medication had been given during this pregnancy nor had there been any complications. In fact, she thought she had a tumor, and due to her obesity it was necessary to confirm the diagnosis of pregnancy by x-ray. She did not bruise easily but her husband reported that he always had. There was no history of a similar episode in any of the siblings.

The baby was discharged on the twenty-eighth day weighing 5,210 grams, 330 grams above birth weight. The platelet count was 100,000 per cubic millimeter. The platelet determinations were as follows:

3/25/44	21,800	4/12/44	113,700
3/28/44	40,800	4/15/44	113,600
3/30/44	72,800	4/18/44	100,000
4/ 2/44	134,200	5/ 6/44	126,400
4/ 6/44	170,500	8/ 2/44	165,000
4/ 8/44	226,000	3/12/45	250,000

The child was returned to the hospital on May 6, 1944, at the age of six weeks. There had been no bleeding or other abnormality. He was more active, cried some, and appeared to be interested in things about him, in contrast to the listless attitude in the first month of life. On physical examination, the findings were normal; the fracture was well healed. The thrombocyte count was 126,400 per cubic millimeter.

On July 31, 1944, he was admitted to the hospital with acute suppurating otitis media which responded well to therapy. A platelet count revealed 165,000 per cubic millimeter.

On his first birthday, March 22, 1945, he was seen again. The mother reported that he had had whooping cough during November, 1944. There had been no bleeding. The present complaint was "ear trouble." Examination revealed subacute otitis media. The parents refused hospital therapy and medical treatment was carried out at home. The clavicle was so well healed that the records had to be consulted to ascertain the site of the old fracture. The thrombocyte count was normal.

Discussion

It would be hazardous to deduce or conclude anything about the disease as it appears in newborn infants. There are only sixteen other available case reports, some of which lack data about the newborn because the main interest concerned thromboeytopenie purpura in the pregnant woman, the baby's case being a minor feature of the presentation. Many of the earlier cases lack laboratory data essential to the diagnosis of thromboeytopenia.

The material from the literature has been summarized in Tables I and II.

TABLE I

CASE NO.	BIBLIOGRAPHY	MOTHER				SEX	WEIGHT	LENGTH	SITTING HT.	SYMPTOMS												
		AGE	PARTY	PURPURA	PURPURA IN OTHER CHILD.					AGE AT ONSET	BLEEDING FROM OR INTO						TEMPERATURE	RUMPEL-LEEDE	SPLENOMEGALY	OTHER		
											SKIN	RECTUM	ORAL MUCOUS MEMBRANE	VOMITUS	URINE	CONJUNCTIVA					VAGINA	
1	Dohrn	40	2	+		F	2,370	43		B*	+		+									
2	Hanot									S†	+		+									
3	Hanot	32		+						S	+											
4	Zangemeister	25	1	+						S		+	+									
5	Mosher	36	6	+	0	F	2,927			B	+											
6	Waltner	30		+		F	1,800			B	+											
7	Liebling	22	1	+		F	3,940			B	+			+	+		+	101°				
8	Greenwald					M				14th day	+	+	+						+	0	Liver enlarged	
9	Siegler	29	3	+		F	4,819															
10	Brown			+			Said to have classic signs and symptoms															
11	Sanford	22	1	+		F	3,608	51	32	B	+			+				101°				
12	Davidson	21	1	+		F	3,470	53		B	+	+	+	+	0		+					
13	Whitney	26	1	+	+	M	2,849			B	+										0	
14	Whitney	28	2	+	+	M	2,424			B	+		+								0	
15	Finn		1	+	+		3,100			B	+			+								
16	Finn		2	+	+		3,100			B	+											
17	Author	34	8	0	0	M	4,880	53	38	B	+	+	+	0	0	+		101°	?	0		

*B—Birth.

†S—Stillborn.

The disease would appear to be transferred from the mother to the child, since all the reports (except our own), which contain information on the subject, mention the presence of the disease also in the mother. However, the recognition of more cases in newborn infants may alter this concept. Possibly, many cases remain unrecognized because of the paucity of data regarding occurrence and manifestations of the disease. Obviously, the disease may occur in a milder form, with such scanty signs that attention is not directed to the blood.

Most cases have involved first-born children. Fifty per cent of the mothers were primigravidas, 25 per cent were secundigravidas, and in two women the first two children were affected.^{13, 17}

The birth weight does not appear significant. The average was 3,107 grams.

Sex would appear to be a factor; there were seven females and four males. However, the prognosis is better in females. Our case is the only reported male to survive (25 per cent), whereas five of the females lived (71 per cent).

TABLE II

CASE NO.	BIBLIOGRAPHY	LABORATORY							THERAPY	RESULTS
		PLATELETS	TOTAL R.B.C. (MILLIONS)	TOTAL W.B.C. (THOUSANDS)	HEMOGLOBIN (GRAMS)	BLEEDING TIME (MINUTES)	COAGULATION TIME (MINUTES)	CLOT RETRACTIVITY		
1	Dohrn								None	Lived
2	Hanot								None	Stillborn
3	Hanot								None	Stillborn
4	Zangemeister								None	Stillborn
5	Mosher								None	Died
6	Waltner	90,000	5.6	8.2	100	12	10	None	None	Lived
					per cent					
7	Liebling	40,000	6.0		110				5 c.c. thromboplastin	Lived
					per cent					
8	Greenwald	30,000	6.1	12.0	20	5	35	None	None	Died
9	Siegler								None	Died
10	Brown								??	??
11	Sanford	20,000	5.8	16.0	18		Normal		None	Lived
12	Davidson	56,000	5.1	42.7	24	3	7	None	60 c.c. citrated trans- fusion. Bothrop antitoxin	Lived
13	Whitney	80,000				1	3.5		20 c.c. transfusion	Died
14	Whitney	90,000	5.5	12.9		11	1.5		55 c.c. vitamins K and C	Died
15	Finn	120,000	5.4			7	3		None	Died
16	Finn	40,000							None	Lived
17	Author	21,800	4.6	19.0	17	1.5	4	1+	100 c.c. transfusion. 0.5 mg. vitamin K	Lived

Practically the only sign is bleeding into the skin or from one of the body portals. Splenomegaly was not reported in a single instance but was noted as absent in four cases. The Rumpel-Leede test was positive only once; it was questionable in our case. Temperatures of 101° F. were recorded in three cases but their significance is unknown. The disease was always present at or soon after birth, except in one fatal case when it appeared on the fourteenth day. This was the only child with a positive Rumpel-Leede's sign and an enlarged liver.

The skin is the most frequent site of bleeding, which takes the form of petechiae or ecchymoses; such manifestations are recorded in 14 cases, or 88 per cent, and no report denies their presence.

The second most frequent site is the gastrointestinal tract, especially the oral mucous membranes where bleeding is more obvious than in the vomitus or stools. Bleeding from the conjunctivae and vagina is less frequent (two cases each). Hematuria is reported once.

The normal platelet count in the newborn is the same as in the adult.¹⁶ It is generally accepted that in the adult bleeding does not occur on the basis of thrombocytopenia unless the platelet count falls to 100,000 or below. The average count in the reported neonatal cases is 58,600 per cubic millimeter. It

appears that the lower platelet counts carry a better prognosis. The average count for the surviving children was 44,333 as compared with 77,333 for the deceased. One child who died and one who survived had counts disagreeing with this concept. With these exceptions, all babies lived who had counts of 56,000, or below, while those who did not survive had counts of 80,000, or above.

In the entire group there were three stillbirths, six children died from the disease, and seven survived. (The outcome in one case is not reported.) This represents 44 per cent survival.

The red blood cell count and hemoglobin determinations are within normal limits for the newborn infant.

Bleeding and coagulation times varied so widely that no conclusions can be drawn. The average bleeding time was 5.7 minutes and the average coagulation time 9 minutes.

The majority of the children received no therapy. Four patients have been treated with transfusions. Davidson gave 60 c.c. of citrated blood but the child continued to bleed until "Bothrop antitoxin" was administered. This child survived. Whitney used blood transfusions in two cases. In the first, 20 c.c. were given and there was no bleeding for two days following the transfusion, but the child died on the third day of intracranial hemorrhage. In the second case, 55 c.c. of blood were given in addition to 1.0 mg. of vitamin K, 100 mg. of ascorbic acid, and 2 c.c. of Koagamin, but the child died twenty-four hours after birth. Our patient was given 100 c.c. of citrated whole blood and 0.5 mg. of vitamin K. The bleeding stopped permanently following the transfusion. Liebling used 5 c.c. of thromboplastin and reports the child normal on the twelfth day.

Postmortem examinations on six infants failed to show any significant lesions except extravasation of blood into various parts of the body.

Summary

A case of thrombocytopenic purpura in a newborn infant is reported. The mother was unaffected. The literature has been reviewed and summarized. It appears that in the newborn the disease is manifested by bleeding (especially into the skin) and thrombocytopenia. The prognosis is poor.

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ACUTE LYMPHATIC LEUCEMIA OCCURRING DURING PREGNANCY

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CASES of leucemia in pregnancy are very rare. Since we have had the opportunity to observe one recently, it was felt that it should be presented; and we believe this report will bring the authenticated cases of pregnancy complicating leucemia to a total of eighty-one. After reviewing the available literature, we have found that the most recent and up-to-date summary of the variously reported comparable cases was made by McGoldrick and Lapp¹ in November of 1943. Including their own case report, they gave a total of eighty authenticated cases of leucemia during pregnancy. Since their article we have been able to find no other reports.

Case Report

The patient was a 23-year-old white gravida ii, para i. Her first pregnancy, which ended in a normal delivery of an 8-pound 3-ounce baby in 1940, was entirely uneventful. The child is living and well at this time. The patient's past history was essentially negative except for tonsillitis in 1940. The second pregnancy began about March 5, 1944, and progressed normally up until June, when she complained of a severe sore throat and was given sulfadiazine medication. At this time her red blood count was 4,000,000 and the hemoglobin 84 per cent. About two months later she was again seen with a severe sore throat, fever, cough, weakness, malaise, and shortness of breath. It is believed that during this period, from June until August, the leucemia began. In August she was again put on sulfadiazine. Five weeks later she was seen again and now had edema, while the previous weakness and shortness of breath persisted. Three weeks later, about November 2, she was admitted to an Army hospital in Georgia, where blood studies revealed her red blood count to be 2,500,000; hemoglobin, 40 per cent; white cell count, 28,000; lymphocytes, 87 per cent; and neutrophils, 3 per cent (see Fig. 2). Physical examination on this date revealed numerous small recent hemorrhages in the conjunctiva, very pale gums, and mucous membranes. There were also a few palpable cervical lymph nodes. The uterus was enlarged to about three fingers below the xiphoid.

Five days later blood studies showed the red blood count to be 1,310,000; hemoglobin, 34 per cent; white blood count 33,950. Differential count showed segmented cells 2 per cent, juveniles 6 per cent, stab forms 1 per cent, myelocytes 45 per cent, premyelocytes 40 per cent, and myeloblasts 11 per cent. Three days after this the patient was given 250 c.c. of whole blood as a transfusion, and was transferred by airplane to Walter Reed General Hospital for possible deep x-ray therapy.

Upon admission to Walter Reed General Hospital the following day (November 11), physical findings were essentially as noted above with the following additions: tonsils were enlarged, the gums were a little swollen and spongy, and two palpable glands were noted at the angle of the jaw. A diagnosis of acute lymphatic leucemia was made. Irradiation was contraindicated. On December 8, 1944, the gums had become markedly spongy and thickened and of a deep-bluish cyanotic color and extended down, almost completely covering the teeth. A small ulcer developed on them at this time. A moderate retinal hemorrhage occurred in the right eye.

The pregnancy itself was progressing normally. The main problem in this case at this particular time was to determine exactly when and how to deliver the patient. Three

possibilities were considered: first, to section the patient as soon as it was felt that the baby was viable; second, to allow the patient to proceed to as near to term as possible and to perform an elective section; or, third, to allow the patient to proceed to term and deliver spontaneously.

The first possibility was ruled out because the patient was responding well to treatment, and we felt that she would probably continue to respond for the next few months. It was also felt that since her disease would obviously terminate fatally, every reasonable chance should be given for a healthy, live baby at term.

The second method of treatment was to be considered seriously in case the patient should develop toxemia or the leucemia should grow worse. This method had been used before successfully by others, as reported by Moloney² in 1943. However, this patient's clinical condition remained good. It was eventually proved that her life would have been materially shortened had cesarean section been performed, as the perineal laceration completely failed to heal and, in all probability, the abdominal incision would likewise have failed to heal.

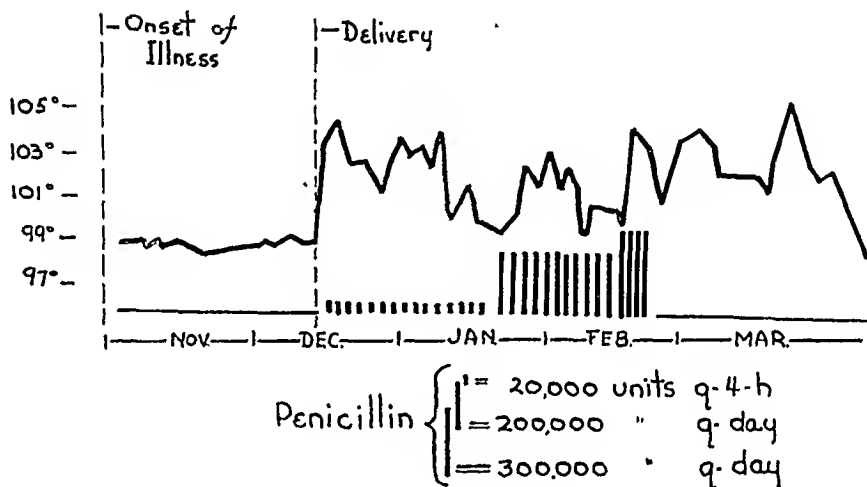


Fig. 1.—Temperature record.

The third method of delivery was decided upon because (1) her clinical course was running quite satisfactorily; (2) she had previously delivered an 8-pound baby quite normally; (3) it was felt that this baby, if anything, was smaller than 8 pounds; and (4) hemorrhage, if it should occur, could be adequately controlled from below.

The possibility of postmortem section was considered and preparations made in the event this should be necessary.

From December 8 to 18 the patient's course was satisfactory. During the foregoing five weeks she had been given a total of twelve whole blood transfusions, and an effort was made to keep the blood picture as normal as possible. About 2 A.M. on December 18 she went into spontaneous labor, which was short and uneventful. After three and one-fourth hours of normal labor she delivered spontaneously a 7-pound, 4½-ounce female infant, which cried immediately and appeared perfectly normal. Immediately following delivery, the patient was given ½₂₀ grain of ergotrate intravenously and 1 c.c. of pitocin intramuscularly. The placenta separated and was expelled intact. Hemorrhage amounted to about 600 c.c. The uterus was packed and the second-degree laceration was repaired with No. 00 chromic catgut, using interrupted mattress sutures. On the following day the packing was removed and was followed by only very minimal bleeding. It was noted at this time that three large hematomas had developed, one in each labium majus and one in the perineum.

The patient's postpartum course, as expected, was very stormy. On the second postpartum day her temperature rose to 104.8° F., at which time she was placed on penicillin therapy (see Fig. 1). Ten days later the perineal sutures were removed. There was no evidence of any absorption whatsoever of the catgut; the lacerated area was infected and

covered with a grayfish fibrin coating and showed no evidence of healing. From the second to the fifth postpartum week, the patient continued to receive frequent whole blood transfusions and penicillin therapy. During this time she made a remarkable clinical improvement. Her gums receded almost back to their normal size, and her blood picture improved temporarily. She lived for one more month, during which time the blood picture took a rapid and sharp turn for the worse in spite of transfusions. Confluent petechiae developed over the medial surface of both lower legs. Her condition gradually became progressively worse, accompanied by loss of weight and general malaise, and she died in a coma on March 25, 1945.

The infant remained in the hospital from the date of her birth until her mother's death. Numerous blood studies consistently revealed normal findings. Upon discharge she weighed over 11 pounds and was perfectly healthy.

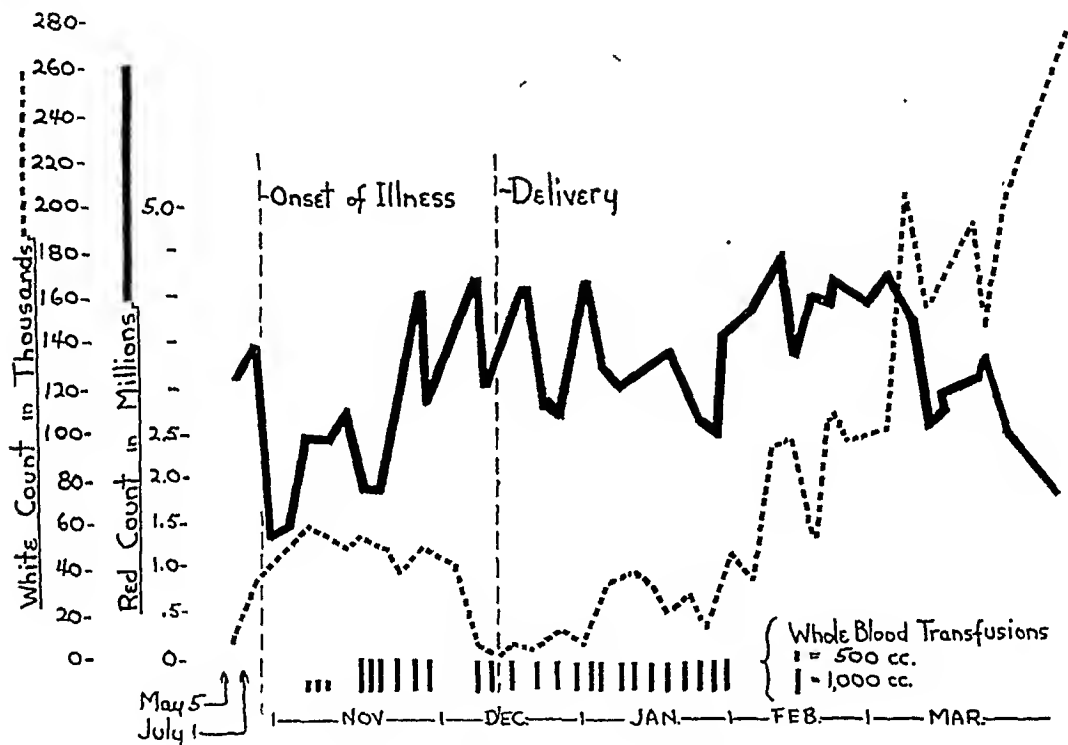


Fig. 2.—Summary of blood picture.

Summary of Laboratory Data and Treatments

A diagnosis of acute lymphatic leucemia was made. X-ray therapy was contraindicated. The patient received a total of twenty-five transfusions, by means of which her blood level was relatively well controlled (see Fig. 2). At the onset of her illness in early May, the white blood count was 8,000. This gradually rose and on November 24 was 56,000. Early in February, it rose to 62,000 and during the last month of her life ranged from about 100,000 to 265,000. Her differential white blood cell study ranged from 85 to 100 per cent lymphocytic cells with the immature young forms ranging from 85 to 95 per cent.

The patient was found to belong to blood group A, her Rh factor was positive, and there was no Rh antibody found. The infant was likewise found to belong to blood group A and to be Rh positive.

During the last three months of the patient's life, she received a total of 3,580,000 units of penicillin (see Fig. 1).

Pathologic Report of Placenta.—Gross: Specimen consists of placenta with membranes and cord intact, which show nothing of significance.

Microscopic: The placenta generally is moderately anemic with no evidence of infarction or leucemic infiltration in the maternal or fetal portions. The cord shows nothing of note.

Diagnosis: Essentially normal placenta showing no evidence of leucemic infiltration.

Autopsy Findings

General.—The body was that of a well-developed, moderately emaciated white woman, 24 years old, whose length was 165 cm. and estimated weight 85 pounds. There was a normal distribution of dark hair on the head and multiple petechial hemorrhages were seen over the skin surfaces, most numerous over the lower arms and lower legs. There was evidence of old subconjunctival petechiae on either side but no recent hemorrhages were seen. The teeth were in good repair, and the mucous membranes were pale, slightly swollen, and exhibited petechial hemorrhages. Lymph nodes in the cervical, axillary, and inguinal regions were enlarged moderately, discrete, and firm. The abdomen was slightly distended and there was an opened, unhealed, postpartum tear in the left posterior quadrant of the vaginal orifice and adjacent perineum. This was covered with a small amount of hemorrhagic fibrinous exudate. The extremities exhibited marked emaciation and slight cyanosis of the nailbeds with the above-mentioned petechial hemorrhages. Rigor and postmortem lividity were marked.

Primary Incision.—Subcutaneous fat over the chest and abdomen was depleted. The musculature was moderately atrophic. On opening the peritoneal cavity, multiple petechial hemorrhages were found on its surfaces, and it contained approximately 300 c.c. of clear straw-colored fluid. The lymph nodes in the omentum and mesentery were enlarged to three to four times the normal diameter, and they were replaced by grayish firm neoplastic material. The nodes along the periaortic region were markedly enlarged, confluent, and formed bilateral masses almost as large as the diameter of the aorta. The liver was 3 cm. below the right costal margin in the midclavicular line and 8 cm. below the xiphoid. The left pleural cavity contained approximately 300 c.c. of slightly blood-tinged fluid, and the right was dry. On both sides the surfaces exhibited scattered petechiae, and on opening the pericardial sac it exhibited similar hemorrhages together with the fluid content of 300 c.c.

Thorax.—Lungs: Right weighed 496 grams, and the left, 414 grams. Their external surfaces were grayish pink and the lower lobes were devoid of crepitation, being rather firm. On section both lower lobes exhibited a rather firm parenchyma with moderate increase in fluid, but there was no evidence of pneumonic consolidation. The upper lobes were essentially normal except for a slight increase in fluid.

Heart: Weighed 248 grams. On its epicardial surface there were occasional scattered petechiae. The myocardium was firm and all chambers were markedly dilated. On the endocardial surfaces of the left ventricle there were several 5 mm. hemorrhages. The valvular structures were essentially normal.

Abdomen.—Liver: Weighed 2,606 grams. It had a light brick-red color with a smooth, dense capsule. On section, the parenchyma was swollen, firm, brick-red, and, other than a 2 cm. grayish nodule in the outer portion of the left lobe, there were no gross evidences of neoplasia.

Spleen: Weighed 1,195 grams and externally over its upper half there was an irregular 6 cm. area of hemorrhage beneath the capsule. The organ was firm and its capsule was pale and tense. On section, an area of infarction in its upper half was found, the area being yellowish and with irregular borders, but it was well circumscribed. The remaining portion of the parenchyma was light brick-red, swollen, firm, and dry. Normal markings were completely obliterated.

Gastrointestinal tract: In the mucosal surfaces throughout they exhibited scattered petechial hemorrhages and a small amount of coffee-ground material was found in the small and large intestine.

Pancreas: Weighed 90 grams, and on section had a light brownish color in contrast to the normal bright yellow.

Kidneys: Right weighed 145 grams and the left, 142 grams. Their capsules stripped easily, revealing occasional subcapsular petechia and pale yellowish smooth renal surfaces. A 1 cm. area of infarction was found in the cortex at the right lower pole. On sectioning, the cortex of either organ was yellowish, pale, and approximately twice normal thickness. The medullary portions, calices, and pelves were essentially normal.

Uterus and adnexa: External surface of the uterus was normal and its size was that of a normal uterus. On opening the uterine cavity it was found to be smooth, grayish, and essentially normal. A small area of brownish pigmentation was seen in the lower third. The Fallopian tubes appeared normal. The ovaries were 1.5 cm. in diameter and flattened, and appeared to be moderately atrophic.

Neck.—The lymph nodes in the cervical regions were moderately large, like those seen elsewhere; otherwise, structures of the neck, including the thyroid, appeared to be normal.

Anatomic Diagnosis.—Leucemia. Postpartum unhealed perineal defect.

Microscopic.—Lymph node: Exhibited extensive replacement of its normal structure by diffuse infiltration of immature lymphoid cells, many of which were lymphoblasts. The sinusoids were filled with these cells and the peripheral sinus was invaded by similar cells. Only a few remnants of lymph follicles remained.

Spleen: Exhibited a similar picture to that seen in the lymph node. The normal structures were largely wiped out, and there was diffuse replacement by a rather dense infiltration of immature lymphoid cells. The Malpighian corpuscles were obliterated for the most part, and there were rather large areas which exhibited areas of early infarction. The appearance was typical of lymphoid leucemia.

Uterus: Exhibited a moderate endometrial atrophy, the glands being rather wide apart and separated by loose stroma. Scattered through the subendometrial areas and deeper muscular layers there were scattered hemosiderin laden macrophages secondary to postpartum involution.

Ovaries: Showed no significant abnormalities.

The kidneys, the adrenals, and the heart showed scattered and minimal areas of infiltration by leucemic cells similar to those seen elsewhere. The appendix, liver, lungs, and diaphragm showed extensive and diffuse lymphatic infiltration.

Comment

The disease in this case apparently began in the first or second month of pregnancy. The pregnancy itself had no obvious effect on the course of the illness. Irradiation therapy in this case was contraindicated when the diagnosis of acute lymphatic leucemia was made, and the patient was carried successfully to term and for four months post partum by successive transfusions of whole blood. Because of the immediate elevation of temperature following delivery, penicillin therapy was instituted, and the patient was given a total dosage of over 3,000,000 units during a period of eight weeks. It is believed that while the penicillin obviously had no direct beneficial effect on the course of the leucemia, it did keep to a minimum the secondary infection of the lacerated perineum and possibly prolonged the patient's life by preventing puerperal infection.

The problem of how to deliver this patient when she was first seen during the last trimester was solved in this particular case by permitting her to carry the pregnancy to term rather than to interrupt the pregnancy and deliver her by section when the infant had obtained a viable age. As has been observed in the past experience of other authors, postpartum hemorrhage, contrary to expectation, was easily controlled.

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WALTER REED GENERAL HOSPITAL

TUBERCULOUS ULCER OF THE VULVA

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TUBERCULOSIS is one of the infrequent diseases affecting the external genitals of the female. Haas¹ noted one case of vulval tuberculosis among sixty-two cases of genital tuberculosis collected over a period of twenty years. Norris² found the external genitals involved in 1 to 2 per cent of cases of gynecologic tuberculosis. Most of the cases were discovered at autopsy and were part of a generalized tuberculosis. Furthermore, few cases have been reported in the American literature. Recently, a case of tuberculous ulcer of the vulva was seen on this service. In view of the rarity of the lesion as well as the end result with therapy, it was decided to report this case.

The patient, B. M., a 35-year-old Negro housewife, was admitted to the Gynecologic Service of Bellevue Hospital on Nov. 9, 1944, with the following complaints: ulcer of right labium minus, weakness and 20-pound weight loss in past year, fever, low back pain, and left sternoelavicular pain.

Past History.—

Medical: Asthma of fourteen years' duration. Syphilis and gonorrhea denied. Patient stated she had never been pregnant.

Surgical: In February, 1939, a total hysterectomy and bilateral salpingo-oophorectomy was performed at a North Carolina hospital. Her admission complaints at that time were dysmenorrhea, oligomenorrhea, and a sense of fullness in the lower abdomen. The discharge diagnosis was bilateral pyosalpingitis. Pathologic examination of the excised tissues was not done. A chest x-ray at that time showed increased density in the hilar regions, but both lung fields were reported as otherwise negative.

Family History.—There was no familial history of tuberculosis or of contact tuberculosis. An aunt had died of breast cancer.

Present Illness.—Four months prior to admission the patient first noticed a "growth" which became larger, and was painful and tender. No bleeding occurred from this area. For the past three months she had suffered from pain in her lower back and in the left sternoelavicular region radiating to the left arm and chest. She also complained of nocturia (two to three times), urgency and burning on urination, as well as a fullness in the bladder after voiding. No gross hematuria was present at any time.

Physical examination revealed a poorly nourished and poorly developed Negro woman appearing chronically ill and showing evidence of marked weight loss. Temperature, 99° F.; pulse, 104; respiration, 24. The chest was symmetrical. A semifluctuant, ill-defined mass was present over the left sternoelavicular junction. Auscultation of the lungs revealed occasional wheezes in both posterior bases. The heart was unremarkable. The abdomen was moderately distended and tympanitic, with a doughy feel. No tenderness was present. No mass was palpable. Some shotty posterior cervical and axillary lymph nodes were present. The inguinal nodes were bilaterally enlarged, firm, and nontender.

Pelvic examination showed a 1 cm. ulcer on the right labium minus. The ulcer was irregular in outline, tender, superficial, moderately clean, with a slightly raised border. There was no surrounding induration. The vagina was foreshortened. The uterus and adnexa were



Fig. 1.—Discrete tubercle formation in floor of vulval ulcer (low power).

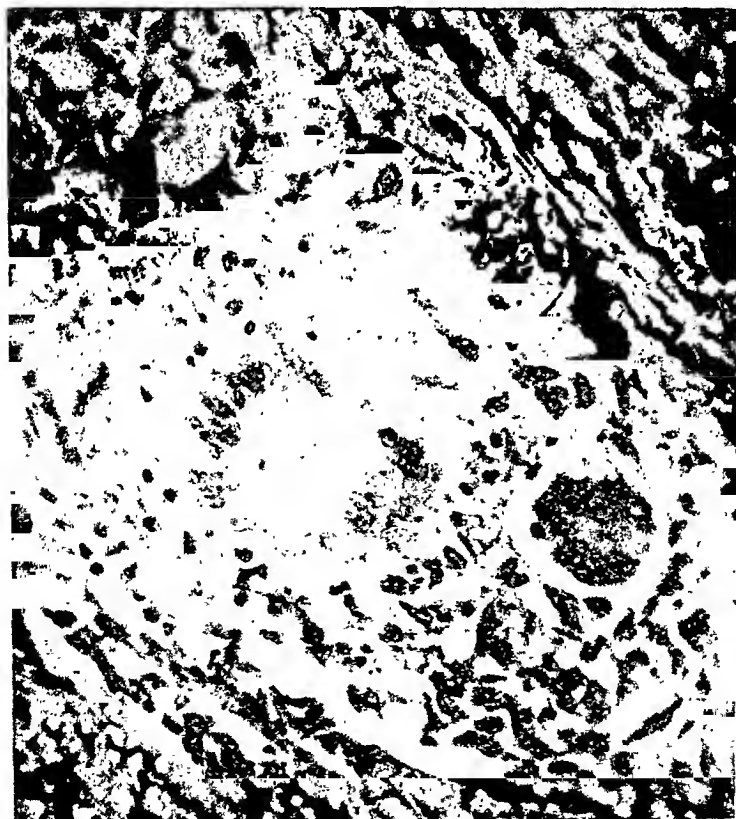


Fig. 2.—Typical giant cells of tuberculosis with peripherally placed nuclei in vulval ulcer (high power).

not palpable, having been removed. Speculum examination showed no cervix to be present. Several small tabs of normal-appearing vaginal mucosa were seen in the vaginal vault, the result of a cicatrix from the previous operation.

Laboratory Data.—White blood cells, 7,300; polys, 66 per cent; lymphocytes, 34 per cent; red blood cells, 4.3 million; hemoglobin, 12.5 grams. Urinalysis and Wassermann reaction were negative. Erythrocyte sedimentation rate was ten minutes. Repeated tests on sputum, gastric contents, and urines were negative for tubercle bacilli. A dark-field examination of the ulcer was negative. The Frei and Ducrey skin tests were negative. Chest x-ray showed enlargement of the hilar shadows and a diffuse scattering of small nodular lesions throughout both lungs. These lesions were interpreted as being due to a hematogenous spread of tuberculosis. X-rays of the hands and feet showed no evidence of Boeck's sarcoid or other pathology. Excretory urography revealed the contrast medium in both urinary tracts with no gross abnormalities.

A provisional diagnosis of tuberculous ulcer of the vulva or early vulval carcinoma associated with a tuberculous peritonitis was made. An attempted aspiration of the fluctuant area over the left sternoclavicular joint was done without success because of lack of cooperation by the patient. No fluid was obtained. On November 16, a block excision of the right labial ulcer was done under novocain anesthesia for diagnostic purposes.

The pathologic report (Acc. No. 2969/44) was tuberculous ulcer of the vulva. Many discrete tubercles with an outer lymphocytic ring and an inner area of granular necrosis were seen. Typical tuberculous giant cells were present with peripherally arranged nuclei and many cytoplasmic processes. (Figs. 1 and 2.) The operative wound healed well by first intention.

The patient ran a morbid course during her hospital stay, with mouth temperatures varying from 97° to 102° F. She was transferred to the Tuberculosis Service, but signed out against advice on Dec. 15, 1944, three weeks after transfer. She stated she was returning to North Carolina. We have been unable to locate the patient since.

Discussion

The question as to whether tuberculosis of the vulva is primary or secondary to a tuberculous focus elsewhere is still unsettled. Although the squamous epithelium of the vulva and vagina is resistant to external inoculation by the tubercle bacillus, tuberculous lesions of the vagina have been produced in guinea pigs by placing virulent organisms in contact with the vaginal walls.³ Furthermore, five cases of tuberculosis of the vulva have been collected by Marc Schmid⁴ suggesting a primary origin. All of the cases occurred very soon after cohabitation. Three of the men had tuberculous epididymitis; the other two had open lung lesions. The occurrence of primary vulval tuberculosis is, therefore, a possibility, but can only be proved by eliminating the probable presence of tuberculosis elsewhere in the body. Jameson⁵ states: "The most minute clinical study with negative findings is insufficient to warrant a diagnosis of primary tuberculosis of the vulva or vagina, for it is often by the microscope alone that one is able to discover tuberculosis in other organs." Secondary tuberculosis of the vagina has occurred by spread from tuberculous foci through the blood, lymph, or by direct extension³ and the vulva is probably involved secondarily in a similar fashion.

The diagnosis cannot be made by inspection alone. There are no typical clinical findings pathognomonic of tuberculous ulcer of the vulva. If the ulcer is of very recent origin and small in size, chancre, soft chancre or chancreoid, granuloma inguinale, and the "primary lesion" of lymphogranuloma inguinale must be excluded. This is accomplished by dark-field studies, serologic tests for syphilis, smears for Ducrey bacilli and Donovan bodies, and the Ducrey and Frei skin tests. When the lesion has been present for a longer time, one must also exclude carcinoma and gumma by histologic sections of a biopsy and

serologic tests for syphilis. Finally, the diagnosis of a tuberculous ulcer is established by the characteristic histologic findings in tissue obtained by biopsy. Forty-eight per cent of patients with genital tuberculosis show evidence of tuberculosis elsewhere.² Suppuration and ulceration of the inguinal lymph nodes may occur. One reported case of tuberculous ulcer was diagnosed by removal of an inguinal lymph node.⁴ Tubercle bacilli may be found in the inguinal lymph glands.⁵ The coexistence of erythema nodosum is also suggestive.⁶

The treatment depends not only upon the extent of the local vulval involvement, but upon the existence and extent of any extragenital tuberculosis as well. Certainly a thorough physical examination supplemented by roentgenologic studies is most essential. General hygienic measures are of paramount importance. Because of the frequency of an associated pulmonary lesion, local anesthesia is most advisable. Small lesions may be treated satisfactorily with curettage and cauterization.⁷ However, the smaller lesions, and often the larger lesions, may be treated best by excision.

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A COMPARISON OF THE COLOR CHEMICAL TEST WITH THE FRIEDMAN MODIFICATION OF THE ASCHHEIM-ZONDEK TEST

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A CHEMICAL test for pregnancy based on the color reaction for pregnandiol (Guterman²) may eventually replace that of the Friedman modification of the Aschheim-Zondek test. The determination can be completed within two or three hours, and the results compare favorably with the Friedman modification of the Aschheim-Zondek test. The chemical test has the distinct advantage over the Friedman test in not requiring rabbits, in being quicker and less expensive.

Method

In our laboratory, we have been carrying out the chemical color reaction test for pregnandiol simultaneously with the Friedman test for pregnancy. The color reaction test is based upon the method for pregnandiol extraction by Astwood and Jones¹ and the color reaction of Talbot and his associates,³ which has been modified by Guterman² for the purpose of ascertaining pregnancy. The method consists essentially of the extraction with toluene of the acid-hydrolyzed pregnandiol complex of urine, followed by the purification and precipitation of the pregnandiol. The characteristic color is developed by sulfuric acid.

The technique of Guterman² is as follows:

A. Hydrolysis and extraction of pregnandiol:

1. One hundred cubic centimeters of urine, 50 c.c. toluene, chemically pure, 10 c.c. concentrated hydrochloric acid, and 2 glass beads are added to a 500 c.c. flat-bottomed Florence flask.
2. The flask is connected via a one-holed cork stopper to a vertical Liebig condenser and the mixture is boiled vigorously over an electric hot-plate for fifteen minutes.
3. The flask and its contents are brought to room temperature by cooling under the water tap.
4. The mixture is transferred to a 500 c.c. separatory funnel, and the lower layer is drawn off.
5. The toluene layer and the toluene-water emulsion are washed twice with 15 c.c. portions of 0.1 N sodium hydroxide and then twice with 15 c.c. portions of distilled water.

B. Precipitation of impurities:

1. The washed toluene and toluene-water emulsion (A-5) are transferred to a 125 c.c. Erlenmeyer flask.
2. The mixture is boiled over an electric hot-plate (in the hood).
3. When the water has evaporated and the toluene mixture is boiling smoothly, 10 c.c. of 2 per cent sodium hydroxide in absolute methanol are added.

4. The mixture is evaporated until one-half of the original toluene volume is reached.
 5. The toluene mixture is then filtered, while hot, through a fritted glass filter (medium porosity Pyrex) with mild suction. (If the filtrate has an orange, pink, or brown tinge, steps B-3, B-4, and B-5 must be repeated until the filtrate is yellow or yellow green.)
 6. The precipitate (B-5) is washed with 15 c.c. hot toluene.
 7. The combined filtrates (B-5 and B-6) are then evaporated to dryness over the hot-plate (in the hood), a gentle air stream being used to drive off the last traces of toluene. This avoids charring of the residue.
- C. Precipitation of pregnandiol:
1. Five cubic centimeters of acetone are added to the residue (B-7), and the mixture is warmed over a hot-plate until the solution is complete.
 2. Twenty cubic centimeters of 0.1 N sodium hydroxide are added slowly while the mixture is still on the hot-plate.
 3. The flask is then placed in an ice-water bath for thirty minutes or in a refrigerator for one hour.
- D. Isolation of pregnandiol:
1. The mixture (C-3) is filtered through a fritted glass filter.
 2. The precipitate (D-1) is washed with 15 c.c. distilled water.
 3. The receiving flask is changed, and 10 c.c. hot absolute alcohol is passed through the fritted glass filter to dissolve the precipitate.
 4. The alcohol filtrate (D-3) is evaporated to dryness over an electric hot plate.
- E. Color development:
1. Ten cubic centimeters of concentrated sulfuric acid are added to the residue (D-4), and the color is observed in a test tube when solution is complete. Colorless to light yellow solution is read as negative. Orange to deep orange brown is read as positive.

We have made a few minor changes in the above technique so that it is never necessary to refilter the toluene mixture containing the impurities, as the filtrate is always yellow in color (B-5). We also find that in using an egg-shaped porcelain crucible, Coors No. 2, that the mixture will evaporate to dryness without charring (B-7).

The technical differences, as compared to the technique of Guterman,² are as follows:

A-4. Allow the toluene layer and toluene-water emulsion to stand until no more urine can possibly be drawn off.

A-5. If the mixture should turn blue litmus paper red after the second addition of alkali, repeat. Then, if the solution is not clear, centrifuge. The clear solution will appear at the top of the tube. After each addition of alkali and distilled water, shake for two or three minutes, preferably in a shaker.

B-1. Transfer to 125 c.c. Erlenmeyer flask the washed toluene and toluene-water emulsion; then pour the supernatant into a similar flask.

B-4. The solution is evaporated until approximately one-half of the original toluene volume is reached.

After the addition of the sodium hydroxide in methanol, the solution becomes cloudy. When precipitation of the impurities is complete, the solution suddenly bubbles up; then boils smoothly. Allow the solution to continue boiling until approximately one-half of this volume has evaporated, before removing from the hot-plate.

Results

The chemical-color reaction test for pregnandiol has been done simultaneously with the Friedman test for pregnancy on 304 patients. Of this number, 262 tests were in perfect agreement: 130 tests showed positive results for both pregnancy tests, and 132 tests showed negative results for both. These findings were borne out by subsequent clinical findings. The results on the other patients did not coincide. Negative chemical tests and positive Friedman tests were obtained on 30 patients diagnosed as threatened abortion. From this group, 22 aborted; 10, however, were given progesterone, and several months later, 8 of the patients were still pregnant. All persons were hospitalized on account of much bleeding. Two patients gave positive results for both tests; then suddenly aborted the following day. There had been no bleeding prior to abortion.

Two patients, we believe, had a persistent corpus luteum cyst that finally degenerated. We did a series of tests, each time obtaining positive chemical and negative rabbit results. After two months, amenorrhea ceased, and a few days later the pregnandiol titer dropped, finally reaching the negative level.

Two cases of hydatid mole were tested. In both instances the chemical test was negative; the rabbit results, positive.

In eight cases, pregnancy was indicated chemically two or three days before it showed biologically. The chemical results were read incorrectly in ten cases.

The table below summarizes the results:

TABLE I

	CHEMICAL TEST		FRIEDMAN TEST	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
*Normal pregnancy	121		121	
Ectopic pregnancy	9		9	
Not pregnant		132		132
Threatened abortion		30	30	
Corpus luteum cyst	2			2
Hydatid mole		2	2	

*Eight from this group gave positive chemical results two or three days before the results were positive biologically.

Discussion and Conclusion

The results which were obtained leave no doubt that there is an equivalent degree of accuracy between the chemical color reaction test and the Friedman test for pregnancy. The chemical test has the advantage over the Friedman test in that a result can be obtained within two or three hours, and that it is more economical. The chemical test plus the Friedman test are good indicators in cases of threatened abortion. The chemical test is negative in threatened abortion due to the fact that there is little or no progesterone being produced. This decrease or lack of progesterone, no doubt, is the cause of the threatening abortion. In contrast, the Friedman test depends upon the anterior-pituitary-like substance elaborated by chorionic villi. A positive

chemical test will be obtained in cases of a corpus luteum cyst but, since such cases are not too numerous and can be differentiated from normal pregnancy by the Friedman test, it should not be a disturbing factor.

I wish to express my appreciation to Dr. C. Arthur Elden for his friendly help and criticism of this work.

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A CONGENITAL ANOMALY OF THE VAGINA WITH PYOCOLPOS

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CONGENITAL atresia of the vagina is usually accompanied by amenorrhea or oligomenorrhea with or without hematocolpos, depending on the functioning capacity of the uterus. These abnormalities cause the patient to seek medical aid early after puberty, whereupon the anomaly is discovered and treated if possible. The following case is interesting because the patient experienced no menstrual difficulty suggestive of her abnormal condition, and also because it contributes further evidence to substantiate the dual origin of the vagina, the upper two-thirds from the müllerian system and the lower third from the urogenital sinus.

Case Report

M. E. R., aged 40 years, an unmarried secretary, entered St. Margaret's Hospital Oct. 27, 1944. (Case history No. 443527.) Measles and whooping cough in childhood. Appendectomy in 1924.

Menstrual History.—Menses began at the age of 13 years, usually lasted eight days, and were regular every twenty-eight days. There was a profuse flow for the first two days. No dysmenorrhea. No metrorrhagia. Menses began to be scanty in June, 1943, and ceased entirely Dec. 15, 1943.

Present Illness.—For ten years the patient had a vaginal discharge which varied from a watery to purulent character. It was never bloody, blood-stained, or black. For the past three weeks it was extremely foul, necessitating the patient giving up her work. During these latter ten years there were occasional attacks of lower abdominal cramps referred to as "gas pains" every two or three months and lasting three days. There was no nausea or vomiting. The bowels were regular. There were no urinary symptoms. For the past three weeks there had been rather steady lower abdominal pain mostly in the midline just above the pubis.

Temperature, pulse, and respiration were normal. Urine was negative. Red blood count, 4,600,000; hemoglobin, 90 per cent; white blood count, 10,000.

Physical examination was negative except for the local findings.

Examination under gas-oxygen Oct. 28, 1944: External genitals were normal. Hymen was normal and the hymeneal orifice admitted a finger. The vagina as felt on digital examination through the hymeneal orifice was a rudimentary closed pouch about one inch in depth and width. On speculum examination it presented a smooth, glistening, pink surface with no apparent point of entrance of a sinus. Attempts at probing for a sinus were unsuccessful. Examination through this vaginal pouch was unsatisfactory for palpation of the pelvis. Rectal examination found the uterus high and apparently normal in size, contour, and consistency. The adnexa were not palpable. Below the uterus was felt a soft, apparently cystic mass extending to the rudimentary vagina.

Diagnosis.—Congenital malformation of the vagina with pyocolpos.

Operation.—Oct. 30, 1944. Spinal anesthesia. Ureteral catheters were inserted prior to operation. A five-inch midline lower abdominal incision was made. The uterus was found to be normal in size, contour, and consistency. Both tubes and ovaries were apparently normal. Extending downward from the uterus was a sac corresponding to the vagina, definitely cystic and very thin-walled in its lower aspect. The bladder and rectum were freed well from the cervix and the vagina, and a complete hysterectomy with excision of the upper vaginal sac was performed. The base of the vaginal sac was markedly adherent

to the dome of the rudimentary lower vagina and was excised with considerable difficulty. This step was considerably facilitated by having an assistant insert one finger into the vaginal sac below and another into the rectum to keep these parts differentiated. During the excision, a small rupture occurred at a thin point in the vaginal sac and a small amount of very foul pus exuded, necessitating drainage from below and through the abdominal wound.

The convalescence was uneventful. The highest temperature was 100.6° F. on the first postoperative day. The temperature ranged from 99 to 100° F. for twenty-one days. The patient's pulse varied from 90 to 100. The patient was discharged on the twenty-fourth day after operation, and there was a continuation of the foul discharge through the lower vagina and the abdominal incision for twelve weeks.

Cultures of the exudate showed *Bacillus coli* and anaerobic *Streptococcus hemolyticus*.

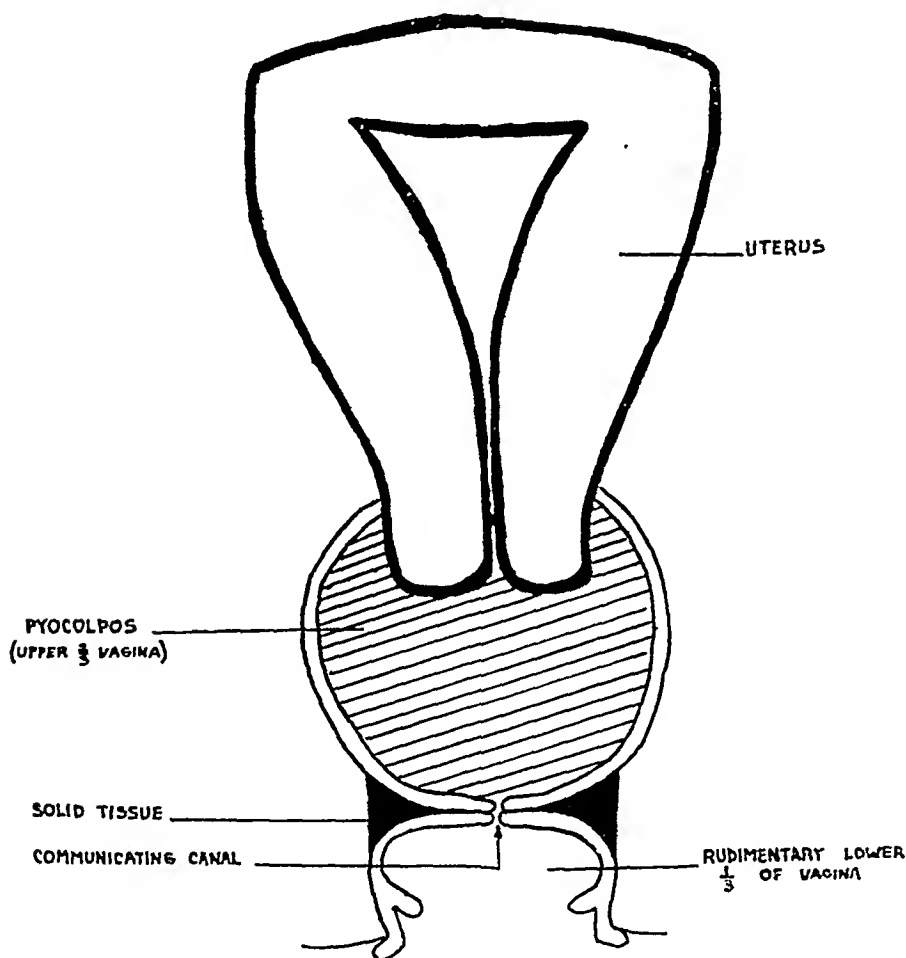


Fig. 1.

Pathologic Report.—Gross—uterus measures 8 cm. in length. Cervix surrounded by long, thin-walled vaginal sac measuring 6 cm. Body of the uterus is small measuring 4 by 3 cm. at the fundus. Uterine canal is 6 cm. long. Endometrium, endocervix, and vaginal mucosa are a peculiar greenish-gray. Myometrium is yellowish-white, firm, and 1.5 cm. thick. External os is small, everted, and shows reddening of the portio epithelium.

Microscopic—Subacute endometritis
 Negative myometrium
 Extreme chronic and acute cervicitis
 Acute and chronic vaginitis
 Pyometra
 Pyocolpos

Comment

The construction of the two vaginal sacs was quite obvious proof of the dual origin of the vagina. The profuse discharge, despite the microscopie opening in the lower vagina was remarkable. The arrest of the vagina at such a late stage in its embryologic development without associated abnormalities in the rest of the female reproductive organs is interesting. When seen so late in life, the best solution seemed to be removal of the entire uterus and the infected upper sac of the vagina. If the patient had been treated earlier, drainage from below with a reconstruction operation on the vagina later could have been effected easily.

A SIMPLE, INEXPENSIVE RESUSCITATION APPARATUS FOR THE NEWBORN INFANT

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ALTHOUGH many factors are listed in all discussions of asphyxia neonatorum, none is as important or as frequent as obstruction of the passageway between the pharynx and the lung.

There is no doubt that hypnotic drugs, general anesthesia, and intracranial damage are all predisposing factors to asphyxia; they not only delay the onset of breathing by depressing the respiratory center, but also abolish the initial cough and crying reflexes which help the child clear its respiratory passages.

If the central nervous system is depressed, the airways must be cleared and artificial respiration instituted until the baby can take over this function itself.

It should be pointed out that none of the so-called respiratory stimulants have a beneficial effect on asphyxia.

Most physicians who deliver babies are well aware of the fundamental principles of infant resuscitation, to which the great majority of babies respond well. These babies, however, are only partially apneic or sluggish. They have good, regular heartbeats, only slight cyanosis, good reflexes, and make occasional attempts to breathe. The ordinary methods of stimulation give excellent results in this group. The difficult group do not respond to the above. These babies are pallid, the heartbeat is weak and irregular, the muscles are flaccid, the reflexes are absent, and the baby makes no attempt to breathe. Intubation and artificial respiration are absolutely indicated if these babies are to be saved.

Many machines have been devised to feed the baby oxygen through an intubation tube. The disadvantages of all of them are that they are expensive, are not portable, and are generally technically difficult to use.

The problem at hand was to find some method of infant resuscitation which was inexpensive, easily transportable, available in times of priorities, efficient, and yet so easy to operate that the general practitioner could use it in the small institution or in the home.

Of all the methods of resuscitation, that advocated by Flagg seems to be the most scientific. The one objection is that the average physician cannot use the direct vision laryngoscope without special training. Yet every practitioner of obstetrics, every registered midwife, every obstetrical nurse, can become familiar with the simple technique of passing a catheter down a baby's trachea. A No. 12 woven silk catheter with its opening at the end is passed along the index finger in the baby's mouth to the base of the tongue. Here the tip of the finger pulls the epiglottis forward. The catheter is pushed down and forward into the trachea. One can be certain that the catheter is in the trachea by feeling the same along the midline of the baby's neck. Once the tube is in place, it can be connected to a suction machine or with an intermediate glass bulb and tubing so that direct mouth-to-mouth suction can be instituted. Thus, the problem of clear passages can be solved.

The problem of artificial respiration with air under controlled pressure requires consideration. Mouth-to-mouth breathing or oxygen without some check on the pressure may cause serious lung damage. In order to control pressure, a very simple apparatus is suggested (Fig. 1). It consists of a series of pieces of rubber tubing connected by two T tubes, and a glass tube 14 to 16 inches long. It can be assembled in any hospital laboratory. The glass tube immersed in 12 inches of water acts as a safety valve. When the pressure of the phy-

sician's breath or the oxygen is greater than 12 inches of water, it will automatically blow off through the water. To make alternate pressure, the finger is put over the open end of the distal T tube at the rate of 16 to 18 times per minute. This forces the oxygen into the tracheal catheter and then to the lungs under controlled pressure. The rate and rhythm should be modified by the physician as soon as the baby makes any attempt to breathe. The newly established rhythm must be followed or the respiratory effort will be depressed.

The above described apparatus costs less than two dollars, exclusive of the oxygen. It can be set up permanently in the delivery room, or can be wrapped in a small package and carried to the home. In the home it can best be used for direct mouth-to-mouth insufflation.

As far as the water receptacle is concerned, a 1,000 c.c. graduated cylinder is advocated, but in the home any vessel more than 12 inches high can be used. The top must be open for the escape of air.

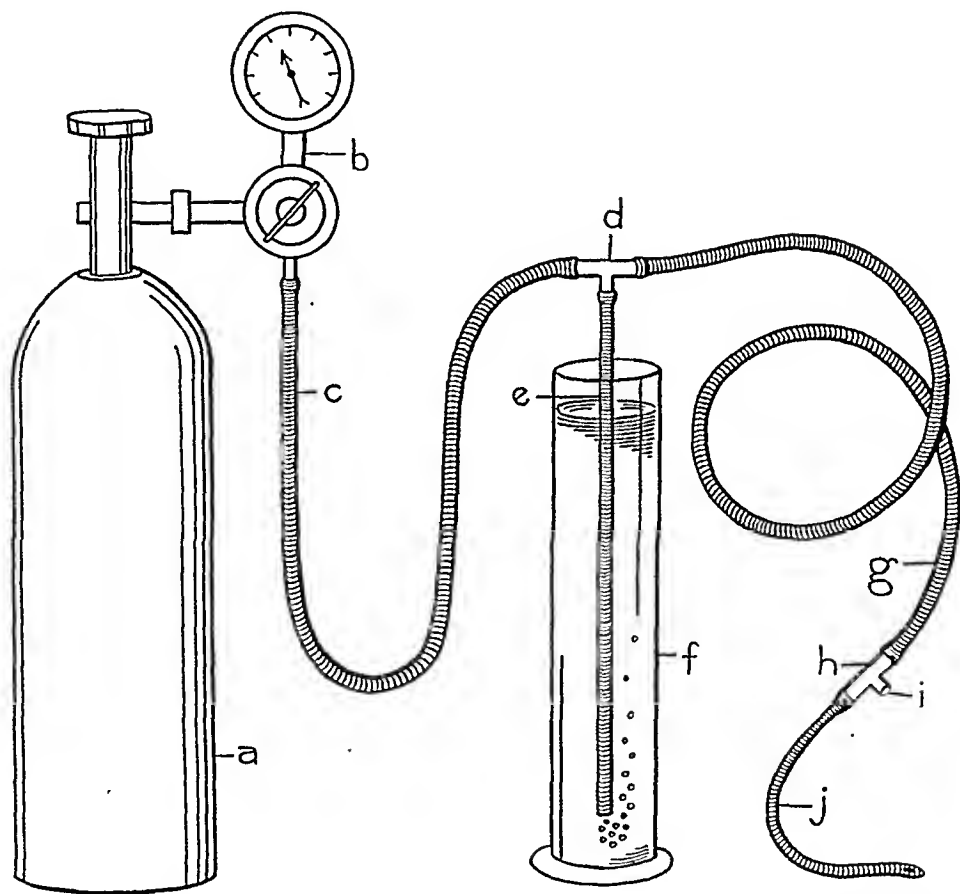


Fig. 1.—A, Oxygen cylinder; B, oxygen regulator; C, length of rubber tubing; D, T tube; E, glass tube; F, water container; G, length of rubber tubing; H, T tube; I, open end of T tube for finger control of inflow of oxygen into tracheal catheter; J, tracheal catheter.

After the baby has established its normal respiration, it may be desirable to give it continuous oxygen for a time to stimulate the respiratory center. The catheter can be withdrawn from the trachea, left in the mouth, and if the opening of the distal T tube is closed with adhesive tape, the baby can get continuous oxygen at the controlled pressure of 12 inches of water.

In the average baby with asphyxia, the apparatus described above has worked well. Its simplicity is such that it can readily be adopted by any practitioner who will take the time to study the diagram and master the technique of tracheal intubation.

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521 PARK AVENUE

EXCRETION OF PENICILLIN IN HUMAN MILK FOLLOWING PARTURITION*

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RECENT reports by Bryan and his associates¹ and by Seeley et al.² have indicated that penicillin is not excreted into bovine milk following intravenous administration. Hodgkinson and Nelson,³ however, recently reported that twenty-four cases of acute puerperal mastitis had been treated successfully with penicillin administered by the intramuscular route. The present investigation was undertaken to determine the amount of penicillin excreted in human milk.

Experimental.—Eleven normal patients seen during the past nine months were selected for study. Penicillin, dissolved in sterile saline, was administered by the intramuscular route two to five days following delivery. Samples of blood were taken for assay one to two hours after the last dose of penicillin. At the same time the breasts were pumped, and milk samples were taken aseptically.

In each case the blood was allowed to clot and the serum was withdrawn with sterile precautions. Serum and milk were stored at refrigerator temperature and assayed for penicillin within twenty-four hours. The method of Dawson, Hobby, et al.⁴⁻⁶ was used throughout. Blood levels ranged from 0.112 to 1.92 units per c.c. Penicillin was present in small amounts (0.015 to 0.06 unit per c.c.) in eight of the eleven milk samples. Slightly higher milk levels resulted from the administration of 100,000 units of penicillin every two hours for a period of six hours than from a single injection of 100,000 units (Table I).

TABLE I. AMOUNT OF PENICILLIN IN SERUM AND MILK FOLLOWING INTRAMUSCULAR ADMINISTRATION

CASES	DOSAGE	SERUM	MILK
		U./C.C.	U./C.C.
1. L. B.	100,000 U. q. 2 h. for 6 hr.	0.46	0.06
2. V. H.	100,000 U. q. 2 h. for 6 hr.	0.96	0.03
3. D. L.	100,000 U. q. 2 h. for 6 hr.	0.96	0.06
4. C. S.	100,000 U.	1.92	<0.03
5. R. H.	100,000 U.	0.48	<0.06
6. M. S.	100,000 U.	0.96	<0.015
7. M. S.	100,000 U.	0.48	0.03
8. R. S.	100,000 U.	0.48	0.015
9. E. B.	100,000 U.	0.48	0.015
10. E. J.	100,000 U.	0.48	0.015*
11. B. T.	50,000 U. q. 3 h. for 24 hr.	0.112	0.007

*Second sample taken four hours after administration of penicillin also showed 0.015 unit of penicillin per c.c.

Summary

Penicillin was administered intramuscularly to eleven normal patients. Three received 100,000 units every two hours for three injections, seven received a single injection of 100,000 units, and one received 50,000 units every three

*The penicillin used throughout this study was supplied through the kindness of Mr. J. L. Smith, Chas. Pfizer & Co., Brooklyn, N. Y.

hours for a period of twenty-four hours. All showed significantly high blood levels one to two hours after the last injection of penicillin. Eight of the eleven patients showed penicillin in the breast milk.

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Editorial

Studies Pointing Toward an Antitoxin for Late Pregnancy Toxemia¹

A HIGHLY toxic euglobulin-like material in the menstrual discharge was first described by Smith and Smith in 1940.¹ Rats killed by this material show generalized vascular damage. The idea that a similar toxin might be operative in late pregnancy toxemia was promulgated by these authors some years ago,² primarily as a result of their studies of the metabolism of sex steroids in women. They pointed out that the local vascular pathology resulting in menstruation is entirely similar to the generalized vascular damage in late pregnancy toxemia and, furthermore, that their quantitative studies of the urinary metabolites of estrogen and progesterone revealed an identical situation at the onset of both menstruation and toxemia, namely, a shift in estrogen metabolism accountable to withdrawal of estrogen and progesterone. Since the same hormonal changes normally precede labor and delivery, they concluded that pre-eclampsia and eclampsia are related to premature deficiency of the placental steroid hormones. Formation of the menstrual toxin is dependent upon hormone deprivation. Withdrawal of hormonal support in pregnancy would theoretically result in the elaboration of a similar toxic component, presumably in the decidua. The onset of labor may well be, at least in part, accountable to this factor. They have found the same hormonal picture in premature delivery. When, as in pre-eclampsia and eclampsia, this occurs prematurely but fails to be accompanied by delivery of the products of conception, sufficient absorption of the toxin might be expected to account for the eclamptic syndrome.

Recently the Smiths have demonstrated marked fibrinolytic activity in the euglobulin fraction of menstrual discharge and have suggested that menstrual toxin, obviously a product of intrauterine tissue damage, may be an intermediary product of the action of a proteolytic enzyme whose release depends upon cellular injury. The venous serum of menstruating and toxemic women has been shown to have the same fibrinolytic activity as that shown by menstrual discharge, whereas similar tests with the serum of nonmenstruating and normally pregnant women were negative. The identity of menstrual toxin with Menkin's more recently described injury factor from canine pleural exudate (termed "necrosin") has been established by means of cross precipitin tests with the serum of immunized rabbits. This finding indicates that the toxin may be elaborated as a result of cellular damage from causes other than hormonal deprivation. It has also provided a means of establishing the presence of menstrual toxin in the circulating blood of toxemic as well as menstruating women, thereby strengthening the original hypothesis that such a toxin is indeed operative in pre-eclampsia and eclampsia.

The venous serum of menstruating and toxemic patients differs from that of nonmenstruating and normally pregnant women and resembles the menstrual discharge not only in that it is fibrinolytic and precipitates the serum of "necrosin" immune rabbits, but also in that it contains a factor capable of prolonging the survival time of rats given a minimal lethal dose of menstrual toxin. This protective factor is concentrated in the pseudoglobulin fraction. Pseudoglobulin fractions of human pleural exudates have been found particularly potent, frequently affording complete protection. Further fractionation and purification of the venous blood of menstruating women and of human exudates is now being performed by Smith and Smith in an effort to localize and concentrate this factor for therapeutic trials. If all elements of danger can be removed, it should provide ideal definitive therapy for combating the toxic component which their studies so strongly indicate is operative in pre-eclampsia and eclampsia.

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Department of Reviews and Abstracts

Selected Abstracts

The Newborn

Gordon, Harry H., and Levine, S. Z.: The Metabolic Basis for the Individualized Feeding of Infants, Premature and Full Term, *J. Pediat.* 25: 464, 1944.

This paper reviews certain data derived from metabolic studies which bear directly on the practice of infant feeding. The authors discuss in detail the relation of water retention to body weight change, calcium metabolism, vitamin requirements of full-term and premature infants. Stressing the appreciation of variations and proper interpretation of their pathogenesis provide the physiologic background for proper individualization in feeding of infants, sick and well, premature and full term.

JAMES P. MARR.

Weinberger, Howard A.: Anomaly of the Peripheral Vessels in a Newborn Infant, *Am. J. Dis. Child.* 68: 405, 1944.

This paper reports a microscopic anomaly in the peripheral vascular system of an infant in conjunction with a death, anatomically attributed to multiple small focal hemorrhages in association with formation of abscesses.

Consideration of the embryologic aspects led to a hypothesis of embryonal maldevelopment of the peripheral vascular tree.

JAMES P. MARR.

Wiener, A. S., Wexler, I. B., and Gamrin, E.: Hemolytic Disease of the Fetus and the Newborn Infant, *Am. J. Dis. Child.* 68: 317, 1944.

Two cases of hemolytic disease of the newborn are described, in which the patients were treated by transfusions of Rh negative blood. In one case, the therapy was dramatically lifesaving, while in the second, in which the disease was apparently milder, the infant died of cholemia and kernicterus.

JAMES P. MARR.

Leach, William, and Holland, Mark: Abscesses of the Lung in a Premature Baby, *Am. J. Dis. Child.* 68: 324, 1944.

The authors report such a case, in a ten-week-old premature infant born six weeks prematurely. The diagnosis was made by the signs and symptoms of pulmonary abscess and x-ray findings.

JAMES P. MARR.

Waddell, W. W., Jr., and Whitehead, Betty Willis: Neonatal Mortality Rates in Infants Receiving Prophylactic Doses of Vitamin K, *South. Med. J.* 38: 349, 1945.

Hemorrhagic disease of the newborn is the result of a low blood prothrombin which may be corrected by the administration of vitamin K. The routine administration of vitamin K as a prophylaxis has eliminated hemorrhagic disease of the newborn. Previous to its use, the incidence of this disease was 0.3 per cent. Vitamin K administration to the mother previous to delivery may materially decrease the incidence of intracranial hemorrhage in the infant. From March, 1940, through December, 1943, 3,775 live infants received 3.2 mg. of synthetic vitamin K intramuscularly immediately after birth. In addi-

tion, 2,879 mothers of these same infants received vitamin K by intravenous or intramuscular injection during labor. During the years 1937 and 1938, 1,429 live infants received no vitamin K. The mortality in both groups was approximately the same. It may be concluded that the routine use of vitamin K will eliminate from the nursery hemorrhagic disease of the newborn, but, apparently, does not greatly affect the mortality rate from intracranial hemorrhage.

WILLIAM BICKERS.

Aldrich, C. A.: *Physiology of the Cry of the Newborn Infant*, Proceedings of the Staff Meetings of the Mayo Clinic 20: 60, 1945.

The author and his colleagues, at the Rochester Child Health Project, have been trying "to study the crying habits of newborn babies under conditions which are imposed on them in a modern hospital nursery, hoping that, with these facts as a basis, we may learn how to meet the physiologic needs of these young individuals better at a most important and critical stage of their growth." The professional group caring for the newborn babies has not been alert to the physiologic needs of these babies, and consequently have been slow in instructing mothers (parents) and others regarding these needs. The problem of the proper management of the newborn is far from solved, since it is a well-known fact that the highest mortality rate among babies occurs during the first two weeks of life. This is the first comprehensive study of this nature that has hitherto been undertaken.

HARVEY B. MATTHEWS.

Radiation

Black, W. A., and Waugh, J. M.: *Successful Resection for Stricture of the Rectosigmoid and Repair of Rectovaginal Fistula Following Radium Therapy for Carcinoma of Cervix; Report of Case*, Proceedings of the Staff Meetings of the Mayo Clinic 20: 87, 1945.

Sufficient irradiation to arrest or destroy cancer of the cervix may cause certain complications of contiguous structures, particularly the rectum and rectosigmoid. The incidence of such lesions is quite high, and should be constantly guarded against. They probably amount to between 5 and 7.9 per cent. The incidence of merely a transitory proctitis runs somewhere around 50 per cent, and subsides in about two months under appropriate care. The chronic or late reactions usually come on about six months after irradiation. There are two types: (1) the intrinsic, in which the reaction is limited to the walls of the rectum; and (2) the extrinsic, in which the reaction is largely in the perirectal tissues. Pathologically, the reaction, as in all irradiated tissues, consists of a fibrous proliferation of the tissues in and around the rectum. Symptoms are mild, moderate, or severe depending, of course, on the amount of irradiation damage done to the tissues. Sigmoidoscopic examination in the intrinsic type readily reveals the lesion; less so in the extreme type but, even here, is of considerable value. In the latter, digital examination reveals perirectal thickening and fixidity to varying degrees. Complications are troublesome and common, especially rectal hemorrhage and stenosis. Treatment depends on the degree of reaction. In the slight and early lesions, soothing enemas are sufficient; while in the late and extensive types, colostomy until healing occurs; or in cases of stricture, colostomy and/or resection is indicated. Rectovaginal fistulae are not uncommon; likewise vesicovaginal fistulae may occur.

The authors report a case in which colostomy was employed 12 years before admission to the clinic for deep "burn" of lower bowel and rectum. They performed a series of operations, including resection of lower part of sigmoid, rectosigmoid, and upper part of rectum with primary end-to-end anastomosis. Three months later a rectovaginal fistula was successfully closed and in four months the colostomy stoma of twelve years' standing was closed. The patient was discharged in good condition.

HARVEY B. MATTHEWS.

Sterility, Contraception

Jakob, A.: Two Cases of Surgical Treatment of Sterility, *Obst. y ginec. latino-am.* 2: 632, 1944.

The author reports two successful cases of plastic operations on the tubes to overcome sterility. Combining these two cases with five previous such operations, the author concludes that at the present time tubal implantation is far from satisfactory, especially in cases of diseased tubes. However, in some cases the operation is definitely indicated.

J. P. GREENHILL.

Hamblen, E. C.: Minimal Standards for Sterility Surveys, *South. Med. J.* 38: 339, 1945.

The first step in treatment of sterile matings is indoctrination of the couple with the scope, aims, time, and cost of the study. The sterility survey can be completed in three visits. The first visit is made between the third and seventh days following cessation of menstruation. At this time, a blood count, urinalysis, serology, x-ray of sella turcica, and basal metabolism are done on both the wife and husband. A gynecologic and endocrine examination is made upon the wife, and a urological study upon the husband. The examination of the seminal fluid includes a study of its physical characteristics, immediate and late motility, survival time, count, and morphology. A postcoital test on the seminal fluid is made upon the wife. A uterosalpingography is performed, the author having preference for this over the tubal insufflation techniques. The patient is instructed in the taking of basal rectal temperatures for the determination of ovulation time. The second visit requires the presence of only the wife, and is made within eighteen hours after the onset of menstruation. An endometrial biopsy is taken and studied for the presence or absence of secretory changes as an indicator of ovulation. The third visit consists of a conference in which the final diagnosis and prognosis, along with therapeutic suggestions, are made. Any tests on the wife or husband which were uncertain are repeated. Occasionally, quantitative studies of the urinary gonadotropin and the urinary 17-ketosteroids are indicated. Testicular biopsy, or testicular and epididymal puncture, may be necessary in cases of aspermia.

WILLIAM BICKERS.

Abortion

McDonough, James F.: Vaginal Bleeding From Potassium Permanganate as an Abortifacient, *New England J. Med.* 232: 189, 1945.

Burns of the vagina and cervix due to the use of potassium permanganate tablets as an abortifacient constitute a new and gradually increasing complication of early pregnancy in and about Boston. The author reports sixty-five such cases; only six patients were successful in producing an abortion, while twelve patients required rigid shock treatment, including blood transfusions because of cervical damage and hemorrhage.

It seems, according to the author, that an attempt should be made to educate the laity that potassium permanganate is not an abortifacient. He points out to physicians the differential diagnosis between threatened and incomplete abortion, and the hemorrhage produced by potassium permanganate.

JAMES P. MARR.

Macias De Torres, E.: Fatal Cases of Induced Abortion, *Rev. españ. obst. y ginec.* 1: 32, 1944.

The author found that, in 1943, the admissions for abortion to his gynecologic clinic of the Provincial Hospital of Oviedo amounted to 17 per cent of the total, and greatly exceeded the admissions for any other individual disorder. Taking into consideration that

90 per cent of the abortions were induced, and that only a small proportion of the women with induced abortions enter the clinic, the importance of the problem becomes evident.

Among the 1,160 cases of abortion there were twenty-seven deaths (2.5 per cent). However, this figure is too low, because a number of patients in desperate condition were taken home where they probably soon died.

Twenty patients (about 70 per cent) died from sepsis due to infected placental remnants. Three types of treatment have been recommended for these cases: conservative, active, and opportunistic, which consists in waiting until the patient remains afebrile for four or six days before proceeding with emptying of the uterus. In all nonfebrile cases, or febrile cases in which there is no adnexal or peritoneal reaction, the author empties the uterus by curettage as soon as possible, and takes additional measures to avoid extension of the infective process. This treatment is evidently the best and gives more rapid results than the conservative method in nonfebrile cases. In febrile cases, the duration of the infection, the virulence of the organisms, the resistance of the patient, and other factors make the difference in mortality for cases treated actively or expectantly too small to deserve consideration, while the active treatment has at least the advantage of shortening the hospitalization in those cases which progress favorably.

Another frequent cause of death is postabortive peritonitis. The use of sulfonamides is justified in these cases; it shortens considerably slight and average cases, but is less effective in severe ones.

The author prefers puncture of the cul-de-sac of Douglas in suspected peritoneal supuration; if it is positive he performs a posterior colpotomy with drainage. If this does not make the collection of pus accessible, he continues medical treatment until he is certain that the pus can be evacuated by another route without risk.

Three patients died from pulmonary embolism due to intrauterine use of soap water or antiseptic solution.

J. P. GREENHILL.

Frühinsholz, A.: Abortion Called "Cervical," *Bull. Soc. gynéc. et d'obst.* 28: 606, 1939.

By cervical abortion, Frühinsholz refers to an abortion in which the immobilized ovum rests in the dilated cervical canal, projecting through the external os, giving to the finger the sensation of a top without the peg or of a small barrel. In a series of 63 cases previously studied, it was found that in 94 per cent of the cases the duration of the pregnancy varied from six to ten weeks. It was not observed after three months and it was more frequent in multiparas (64 per cent). Eleven of the 40 multiparas had had more than five children. In most of the cases there is perhaps excessive softening of the lower uterine segment. The uterine contractions force the ovum into the dilated isthmus as a sort of hernia. The so-called cervical abortions are in reality cervico-isthmic or cervico-segmentary abortions. Since by the time the ovum reaches the cervix, the abortion has been accomplished, there is little pain, few uterine contractions, and not much bleeding. The condition is not serious. In only one in ten cases is the ovum expelled from the cervix spontaneously, hence intervention is necessary in most cases.

J. P. GREENHILL.

Malignancies

Mattos, S. O., and Menzen de Bodoy, C.: Sarcoma of the Uterus, *Am. brasil. de ginec.* 18: 192, 1944.

Unlike carcinoma, sarcoma of the body of the uterus is more common than that of the cervix. Many authors ascribe this to the correlation between sarcoma and myoma. From the etiological viewpoint, sarcoma of the corpus has been grouped as follows: sarcoma developing in an otherwise normal organ (primary sarcoma) and sarcoma originating from a pre-existing myoma (secondary sarcoma or degenerated fibromyoma) the latter being by far the more frequent type. The secondary sarcomas may develop in: (1) submucous myomas, either forming a polypoid tumor with a portion of the mucosa intact, or

invading the entire mucus; (2) in subserous myomas; (3) in intramural myomas, forming circumscribed tumors, or interstitial myomas, where they are difficult to differentiate from primary sarcomas. Robert Meyer suggested the following histologic classification of sarcomas: sarcoma of the muscular cell (malignant leiomyoma, malignant myoma); fusocellular sarcoma, round-cell sarcoma, and special forms (alveolar sarcoma, angiosarcoma). The average incidence of sarcomatous degeneration of myoma, as given by statistics in the literature, is 0.76 per cent. Whereas primary sarcoma occurs usually in women past the menopause, secondary sarcoma occurs in younger women.

The clinical diagnosis of sarcoma of the uterus is difficult. The rapid growth of the tumor, presence of a sero-sanguineous discharge from the vagina with a fetid odor due to secondary infection, and emaciation of the patient should arouse suspicion of sarcomatous degeneration. Pain is an early symptom in sarcoma, ascites is often present, and fever is more frequent than in other malignant tumors of the uterus. The prognosis must be guarded because of the possibility of local recurrence. The authors favor radical operation whenever feasible. The prognosis is more favorable in circumscribed forms which are amenable to surgery and radiotherapy. The more rapidly growing tumors are of the primary type and are radioresistant.

The authors report seven cases of secondary sarcoma in women 29 to 49 years of age. One of these was considered inoperable and was given radiotherapy alone; all others were operated on and irradiated postoperatively. All the patients have been observed for one, two, and more years, and all, including the inoperable case, are in good condition.

J. P. GREENHILL.

Nomirovsky, J.: Cancer in Women and the Androgens, *An. bras. de ginec.* 10: 136, 1945.

The author first discusses the value of the androgens in the prevention of spontaneous cancer in rats and the importance of castration following operation for breast cancer. On the basis of the beneficial effects observed in such cases, the author bases his rationale for the use of androgens in carcinoma in women. He reviews the literature on this subject and gives a report of eight personal cases. He confirms the analgesic effect of the male hormone and also the improvement in the patient's general condition. These effects it is true are temporary. The dose given was 25 mg. every second day.

J. P. GREENHILL.

Cohn, Theodore D., and Cohn, Harold: Low-Back Pain as Presenting Symptom of Malignant Breast Tumors, *New England J. Med.* 232: 342, 1945.

The prime purpose of this paper is not only to reiterate and emphasize that spinal metastasis from an unrecognized breast tumor may be the cause of chronic low-back pain.

The authors report and discuss four cases of carcinoma of the breast in which pain from metastatic foci to the spine and bony pelvis was the first evidence of neoplastic disease.

JAMES P. MARR.

Haber, J. J.: Conization and Early Diagnosis of Carcinoma of the Cervix, *Am. J. Surg.* 67: 68, 1945.

Conization of the cervix as a procedure combining both diagnosis and treatment is recommended by the author in cases of chronic cystic cervicitis and those where "amputation, Sturmdorff's operation, and trachelorrhaphy are indicated." It can be employed in three ways: slight, moderate, and radical, depending upon the quantity of tissue to be removed in the individual case. Among 311 conizations performed, eighteen showed malignancy, and eleven, squamous cell metaplasia on pathologic examination. It is also advocated as a routine procedure in cases in which supravaginal hysterectomy is to be carried out. As a method of biopsy, it is claimed that conization is a more thorough means of obtaining an adequate specimen.

FRANK SPIELMAN.

Cesarean Section

Habeeb, Alfred, and Elliott, Hiram R.: Cesarean Section Under Spinal Anesthesia, *South-ern M. J.* 38: 381, 1945.

The use of inhalation anesthesia in cesarean section practically always necessitates resuscitation of the baby. Spinal anesthesia produces marked relaxation of the abdominal wall and thereby shortens the operating time. The babies rarely require resuscitation. Operative bleeding is reduced because of the better motility of the uterus. The ideal age group for spinal anesthesia is under 30 years of age. The authors prefer the use of pontocaine in a dose of 12 to 15 mg. The spinal anesthesia is administered through the third lumbar space. Drop in blood pressure was controlled by the administration of "ne-synephrin."

Contraindications for spinal anesthesia are those patients with pathology of the spinal cord, infections of the skin, septicemia, and psychic disturbances. Hemorrhage and anemia are always contraindications of spinal anesthesia.

WILLIAM BICKERS.

Orengo Diaz del Castillo, F., and Martinez Jimeno, A.: Genital Tumors as Cause for Cesarean Section, *Rev. españ. obst. y ginec.* 1: 239, 1944.

Among 591 cesarean sections performed at the Santa Cristina Maternity Hospital of Madrid, the authors found eleven cases in which myoma or cyst made delivery impossible and one case in which cervical cancer was the reason for the intervention.

Myoma is rarely an obstacle to delivery. When it is, abdominal cesarean section is indicated after a cautious period of awaiting which unfolds the lower segment. The incision is made in this segment unless it contains myomatous nodules which make the classical incision advisable. Myomectomy follows if there is no infection. In suspected cases or in those with several fibromyomas, or if the woman is a multipara and near the end of her sexual life, subtotal hysterectomy is performed. Another possibility is to do only a cesarean section and leave extirpation of the tumor for a more opportune time, but this conduct is better avoided except in young women in whom enucleation of the tumor implies risks due to great difficulty of the operation or to infection. When the fetus is dead and there is infection, the uterus is removed without opening it. Total hysterectomy is not justified unless the myoma is implanted on the cervix. In the present series, cesarean section was performed in four cases, subtotal, and total hysterectomy in one case each, and myectomy in two cases. There was no maternal mortality, but two fetuses died.

Ovarian cysts offer an obstacle to delivery even less frequently than fibromyomas. The modern treatment of labor complicated by obstructing cyst is abdominal cesarean section followed by extirpation of the tumor; this was done with excellent results for mother and child in the two cases of the series. Attempts at displacement should be rejected; they cannot succeed when there are adhesions resulting from torsion of the pedicle, and this complication is frequent during pregnancy.

There was one carcinoma of the cervix which illustrates what should be done when the tumor is discovered in the third month of pregnancy; application of a moderate dose of radium (about 3,000 mg.h.), later a Porro cesarean section, and irradiation after the puerperium. The preliminary use of radium offers the advantages of inhibiting growth and extension of the tumor and of attenuating or suppressing the infection.

J. P. GREENHILL.

Gynecology

Medina, J., Amorim, M. F., and Netto, A. Wolff: Two Cases of Brenner Tumor, *An. brasil de ginec.* 18: 176, 1944.

Brenner tumors belong to the group of ovarian neoplasms designated by Greenhill as "special tumors" and to which Novak gave the generic name of "dysontogenetic tumors." Histologically, these tumors may be classified as adenocystic fibromas with Brenner type

epithelial inclusions. Depending on the predominance of the fibrous or the epithelial component, the tumors may be solid or cystic, the latter being extremely rare. With a few exceptions, Brenner tumors occur in women past the menopause. The incidence of these tumors is low. Among 48,000 ovarian tumors, Novak found 19 tumors of Brenner type, a rate of 0.039 per cent. Without microscopic examination, the solid type may be confused with fibroma of the ovary, and the cystic type, especially when the fibrous nodules are very small, with cystadenoma. The histologic characteristics of Brenner's tumor are nests of epithelial cells surrounded by fibrous connective tissue. The tumors present no special clinical symptoms other than those of a cystic or solid tumor of the ovary. Contrary to the granulosa tumors and arrhenoblastoma, they do not exhibit any endocrine activity. They are essentially benign, both clinically and histologically; they grow slowly and do not impair the general condition of the patient. Extirpation usually results in cure.

The authors present two cases of Brenner tumor of the fibrous type, in women 49 and 62, respectively, together with complete clinical histories, histopathologic findings and microphotographs. Robert Meyer's hypothesis, which considers Brenner tumors as originating from Walthard cells, is also subscribed to by the authors.

J. P. GREENHILL.

Rodrigues, F. C.: About a Case of Tuberculosis of the Cervix Uteri, *An. brasil de ginec.* 10: 35, 1945.

The author reports a case of tuberculosis of the cervix uteri in which the symptoms were profuse serous discharge, asthenia, pallor, and loss of weight. The patient's physician suspected a carcinoma and sent her to the author. Biopsy revealed the true diagnosis. The cervix was then amputated and the endometrium curetted. The curetted material showed tuberculosis. The operation was followed by irradiation therapy. However, pulmonary tuberculosis appeared and this was followed by involvement of the intestines and the kidneys. The patient died.

J. P. GREENHILL.

Rieper, J. P.: Auxiliary Method of Diagnosing Lesions of the Uterine Cervix, *An. brasil de ginec.* 10: 63, 1945.

The author recommends that vitamins A, C, and D be applied locally to the cervix in order to differentiate between benign and malignant conditions. The lesions which clear up in a few days after the application of the vitamins are definitely benign and they are in the majority. Where the cervical pathology does not disappear, a biopsy should be performed to determine the exact diagnosis.

J. P. GREENHILL.

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VAGINAL AND CERVICAL CYTOLOGY IN UTERINE CANCER DIAGNOSIS*

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THE question of whether or not any worth-while diagnosis of uterine cancer may be made by a vaginal smear is the subject of some speculation. We have often talked of finding cancer cells in the smears, but have seldom been able to demonstrate the weird and colorful cellular phenomena manifested in cancer cytopathology.

I, personally, have found the study of cancer cytology fascinating, and I trust that these color photomicrographs prepared from our own series of cases will prove of interest. I would like to pay tribute to Dr. George Papanicolaou, Professor of Anatomy at Cornell University,¹ who had for years studied the histology of the cells desquamated from the genital tract, and in occasional cases found strange bizarre forms appearing, different from any other cells he had ever seen. After collaborating with Dr. Traut, the pathologist, together they published an excellent monograph entitled *The Diagnosis of Uterine Cancer by the Vaginal Smear*.² Since that time Meigs,³ Ayre,⁴ Jones and Neustadter,⁵ and various other investigators have studied large series of cases, reporting accuracy in diagnosis to within 5 to 7 per cent.

*Presented at the First Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, held in Montreal, Quebec, June 15, 1945.

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The principle underlying the hypothesis is that the epithelium arising from Müllerian ducts possesses the characteristic of desquamation, and the cells thrown off pass down the physiologic stream through the tubes, uterine cavity, cervix, and vagina. Malignant growths arising from these organs are, with few exceptions, exfoliative growths. Therefore, desquamation from these lesions is much greater than from normal epithelium, and in the blood and secretion from the moist friable surface of a cancer lesion are to be found cells which would appear to be morphologically malignant. These secretions may be readily aspirated as a smear or spread, which may be taken wherever the patient is first seen, in the office or in the clinic, so that the element of delay is eliminated. This is most important, as statistics have shown that a period of about eight months is usually lost between the appearance of the danger signal, metrorrhagia, and the confirmation of malignancy by surgical biopsy. In uterine cancer this delay probably shifts one-third to one-half of the cases from the curable into the hopeless bracket.

Most gynecologists agree that it does not take the judgment of an expert to diagnose cancer when the lesion presents the appearance of a huge ulcerating growth invading the adjacent structures. Even a biopsy is not necessary here, except to confirm an obviously correct clinical diagnosis. In such advanced lesions the confirmation may readily be made without trauma by means of the cytology test. In clinically doubtful cases it presents a simple method of differentiating between the metrorrhagia of the menopause and the bleeding of an early cancer lesion which may be so minute as to be not detectable by the expert eye or finger of the examiner. That this is possible has been demonstrated recently in "Test Case to Show the Value of Cervical Cytology Smear in Uterine Cancer Diagnosis,"⁶ and in numerous other cases which we have encountered. The clinical appearance in these cases was typical of an erosion, but the cell smear labeled them malignant, confirmed subsequently by biopsy.

The term "vaginal smear" is regrettable, as it suggests a bacteriologic smear. We speak of a cytology smear and modify it as being vaginal or cervical. The cytology smear is really a "surface biopsy." It may be compared to raking a lawn. The leaves raked up are dead and shrunk, but they still possess the same identity of structure as the mother plant. Similarly, in cancer the cells carry the stigmas of the disease. In the smears a diagnosis is made chiefly on the basis of the characteristics of the abnormal cells found. While a cellular diagnosis may be made, this is certainly less authentic than a tissue diagnosis where invasiveness may be assessed. Nevertheless, evidence and experience of expert cytologists would point to the conclusion that enough circumstantial evidence is usually presented to permit a reliable presumptive diagnosis to be made in over 90 per cent of the cases studied.

During the course of our studies of vaginal smear cytology,* we found it advisable to modify the original technique of Papanicolaou and Traut, because we found that cytology smears taken routinely from the external os of the cervix exhibited a greater concentration of cancer cells.⁴ Therefore, in clinically

*This work assisted by a grant from the Banting Research Foundation.

MORPHIOLOGY OF NORMAL AND MALIGNANT SQUAMOUS CELLS

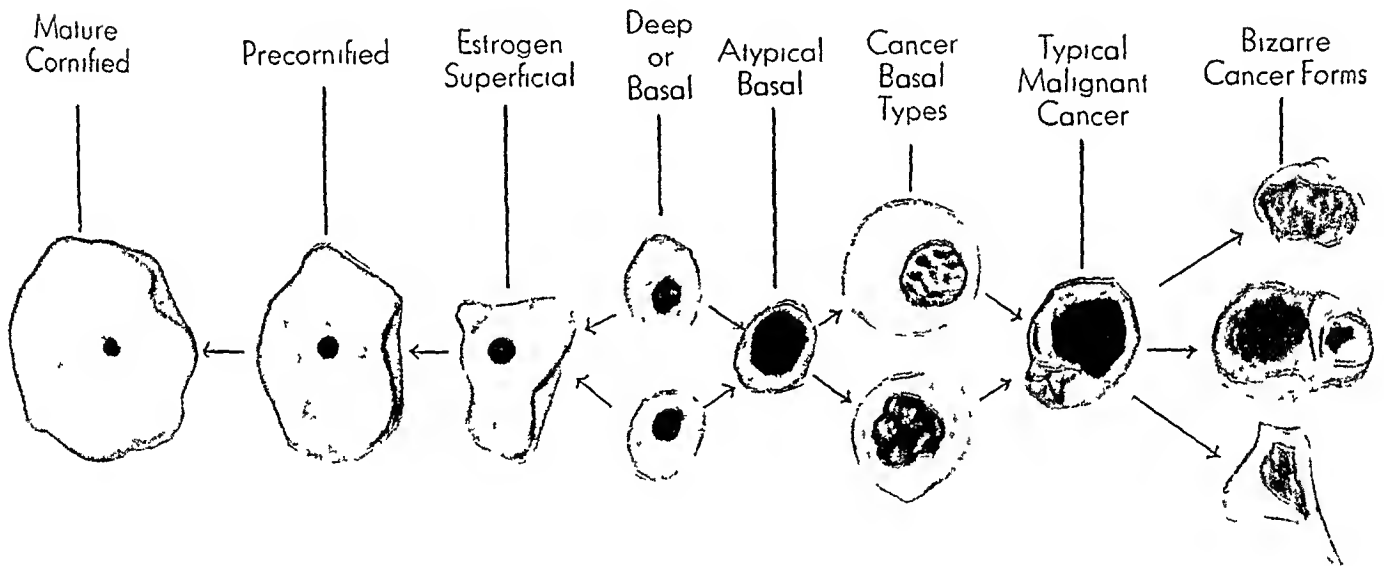


PLATE A

Graphic representation of cell types showing normal stages of growth from the basal cell to the mature cornified cell under the influence of the growth-promoting estrogenic hormone. This is contrasted to malignant growth in the opposite direction showing increasing degrees of cellular atypicalness, from the more mature cancer types to the more embryonic with bizarre-appearing forms.



suspicious cases, smears taken directly from the cervical os gave a more rapid and more efficient identification of the malignant cells. This would seem a logical procedure because over four-fifths of the genital malignancies do arise from the cervix or from the endometrium. In the case of a cervical malignancy the smears are taken directly from the surface of the growth, while in the case of a fundal carcinoma, a larger number of the malignant cells will be found in the mucus at the external cervical portal than would be disseminated over the more capacious vaginal floor.

The cytology of the cervical canal is considerably different from that of the vagina. In malignant cases we find fewer of the normal squamous epithelial cells and a greater quantity of mucus and leucocytes, but more significant, a greater concentration of malignant cells is found. It has been our conclusion that it is well worth the extra effort of inserting a speculum to take the smear from the external os rather than to rely upon the more haphazard method of taking a smear from the vagina which might possibly come from a clean side wall or from the roof of the vagina, missing the more concentrated mucus exuding from the external os onto the floor of the vagina in the region of the posterior fornix.

It has been our experience that a diagnosis of malignancy of the endometrium can be reliably determined by the smear method (see Plate C, 1 to 3), but there is slightly greater risk of error in this type than in cervical malignancy. The epithelium of the uterine cavity does not desquamate to the same extent as the squamous epithelial surfaces. Exfoliation from the endometrium occurs normally during menstruation and abnormally in the presence of any degenerating or necrosing or bleeding lesion. Certain types of fundal malignancies are diagnosed as such by the pathologist, chiefly on the basis of their morphologic structure or pattern, while the individual cellular morphology may appear to be within the limits of a benign hyperplasia. An excellent example of this is the adenoma malignum of the endometrium or of the cervical canal. Another factor that accounts for a greater percentage of error in the cytology diagnosis of fundal malignancy is the fact that so many lesions occur which are on the borderline between extreme endometrial hyperplasia and adenocarcinoma. In many such lesions different pathologists would render different diagnoses. Therefore, such a situation is bound to increase the percentage of error in the cytological diagnosis.

It is well known that any cutting operation through a cancerous lesion carries with it the hazard of trauma, bleeding, and lymphatic extension. Many suspicious lesions require surgical operation solely for the purpose of confirming the nature of the lesion by biopsy. In many of our cases we have found it practical when faced with a clinically suspicious lesion to confirm the malignancy preoperatively by a cytology smear. Then, following a positive diagnosis, do the biopsy and at the same time insert radium for therapy. Therefore, a surgical procedure is often completely eliminated and the danger of added trauma, bleeding, and lymphatic spread avoided.

In our series, we have encountered a number of cases where the presence of sepsis presented a definite contraindication even to a surgical biopsy. However, smears could be taken immediately without stirring up the infection. We have

found this factor of assistance in differentiating between a degenerating myoma and a fundal carcinoma with secondary infection.

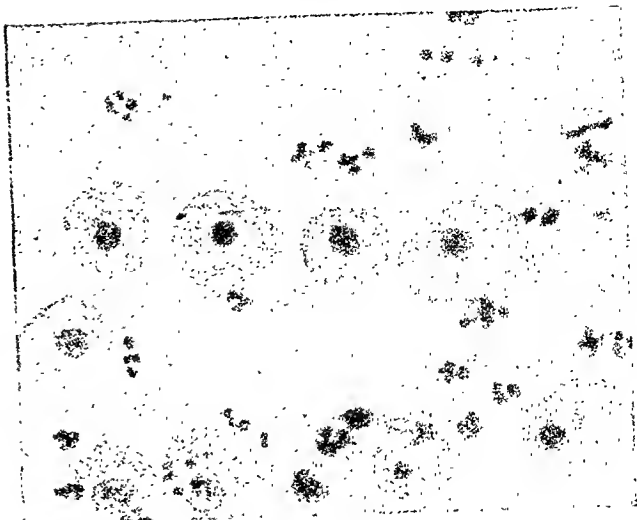
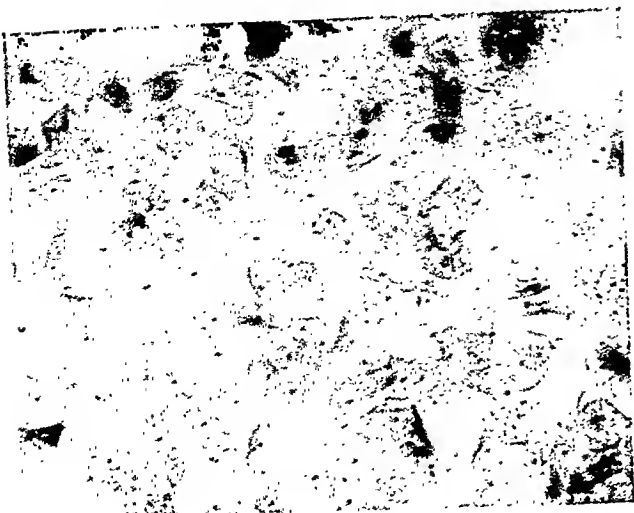
Some of our patients when first seen were known to have a positive Wassermann test, and in the presence of a cervical lesion clinically suspicious for malignancy, the smear has rendered helpful differentiation. Syphilitic lesions have been found negative for cancer cells, of course, while a malignant lesion will show cancer cytology, presenting a rapid differential diagnosis.

Economic considerations may not be overlooked. A smear may be taken in the office or clinic at a cost of \$5.00 or less. A biopsy means hospitalization and an operation which may cost \$100 or more. The chief contribution of the smear technique is its ability to pick up the telltale malignant cells at a time when the cancer may be too small to be seen or to be felt by the eyes or the fingers of the expert examiner, and where only the symptom of "spotting" of blood gives the physician a suspicion of what is developing. He will naturally hesitate to advise hospitalization and operative therapy until he has something more tangible than just a symptom. Before this evidence may become apparent clinically, valuable weeks or months may be lost. Cytology smears taken at the time of the first suspicious symptoms would help to differentiate between an innocent menopausal origin and a malignant cancerous lesion. Therefore, the smear cytology test will diminish the factor of delay and will obviate unnecessary hospitalization and expense except in those cases where a positive or suspicious result calls for an immediate confirmation by biopsy, and adequate treatment of a lesion still in a curative stage.

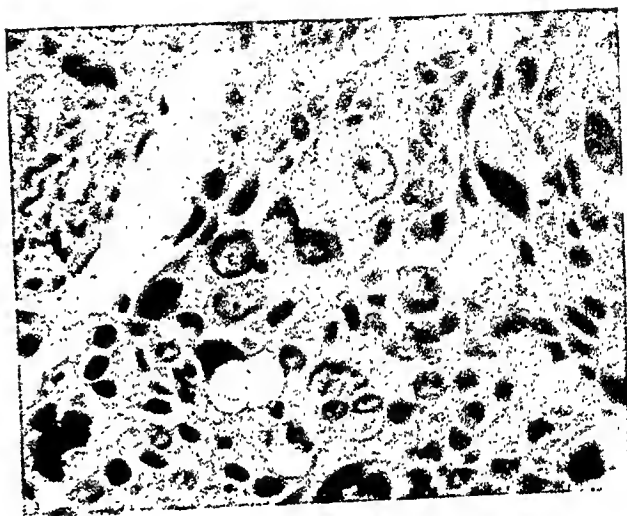
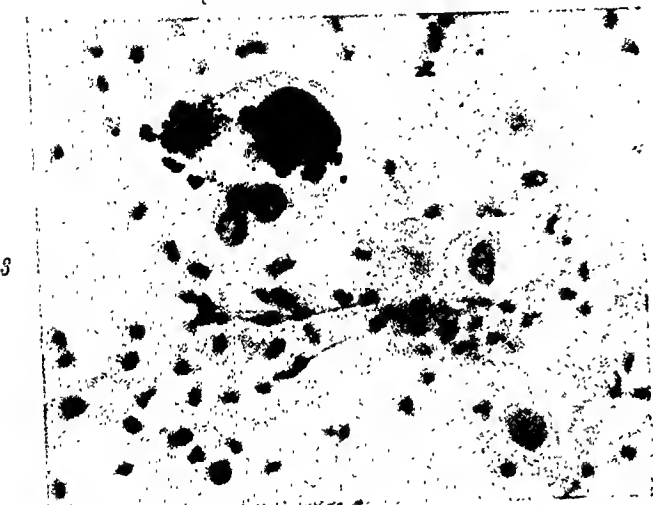
In following up our patients who have been treated with x-ray or radium, Dr. W. A. G. Bauld, Chief of our Women's Cancer Clinic, has indicated that he finds the cytology smears of value in assessing therapy. Many cases will show a raw area on the vaginal portio which may be slow to heal and may bleed slightly on examination. Some of these cases show cancer cells in their smears while others do not, yet the clinical appearance in both may be identical. While we are learning more every day, a great deal is yet to be learned regarding cellular changes resulting from radiation. We do observe certain characteristic effects, viz., reversion of cell type from the more embryonic bizarre cancer forms to the more mature types, while nuclear fragmentation and shrinkage with vacuolation of the cytoplasm are often noted.

Centrifuge Cytology Technique

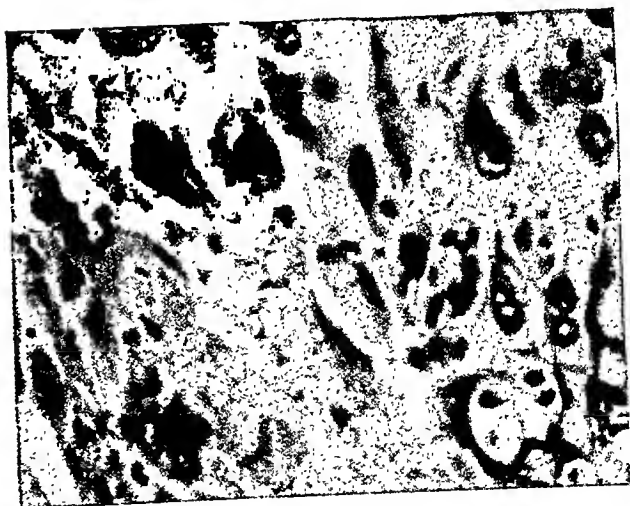
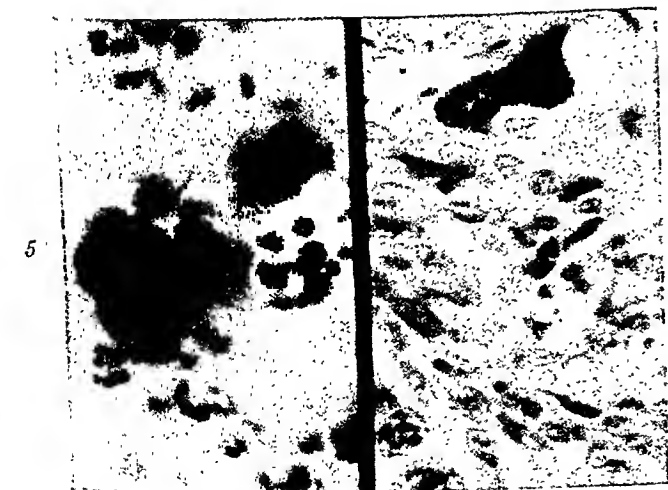
Certain factors tend to limit the scope of adaptability of the smear tests, viz: (1) the slides cannot be mailed in ether and alcohol, and drying destroys the cells; (2) staining is not simple, requiring a specialized technician. As the slides are loose in a bottle, jarring frequently causes much of the secretion to be washed off, permitting part of the diagnostic material to be lost. Quite by accident we stumbled onto a different cytology test, the centrifuge test.⁷ By gathering up the sediments from the bottom of the bottle, it was realized that this sediment contained the telltale cancer cells which when placed in a corked test tube in a few drops of fixative solution could be at once fixed and preserved and then mailed just as easily as a Wassermann test. As many of the cervical aspirations were rich in blood and secretion, the specimen was centrifuged, then mounted in paraffin, sectioned, and stained with hematoxylin and eosin. In taking the test, the cervical secretions are aspirated and placed in a test tube. The results were highly gratifying as, instead of the



2



4



6

(a)

(b)

PLATE B

1. Vaginal cytology smear taken during proliferative phase in a normal case. The cornified cells are numerous, indicating a normally active estrogenic secretion. (Low power.)
2. Vaginal cytology smear from a menopausal woman manifesting bleeding. The cells are all of the basal type, indicating estrogenic deficiency. Note the nuclear uniformity. (High power.) Such a picture in the smear gives a presumptive diagnosis of benign bleeding.
3. Cervical cytology smear showing cancer cells aspirated from the external os in a case of squamous carcinoma of the cervix. Note the extreme nuclear variability.
4. Tissue biopsy in same case of squamous carcinoma of cervix. Observe the same cellular variability as seen in the smear.
5. (a) Cervical cytology smear in case of 26-year-old woman admitted to the ward bleeding. Note bizarre cell with nuclear multilobulation.
- (b) Tissue biopsy from same case of squamous carcinoma of cervix showing the same types of cells in the tissue.
6. Centrifuge cytology technique showing large numbers of malignant cells segregated by the centrifuge. This is not a biopsy but simply an aspiration of the cervical secretions. (High power.)



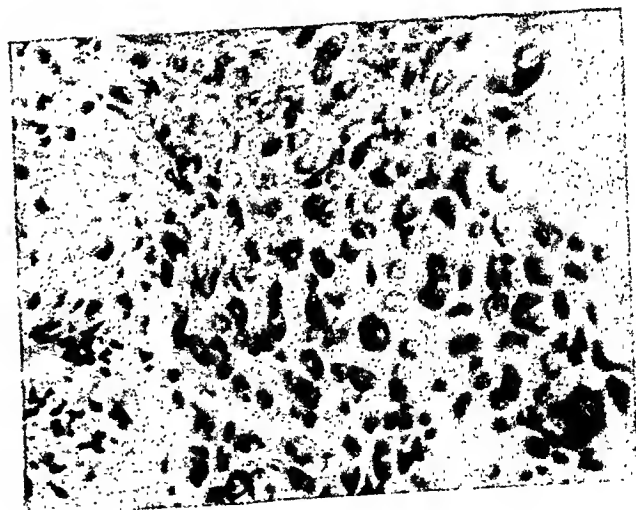
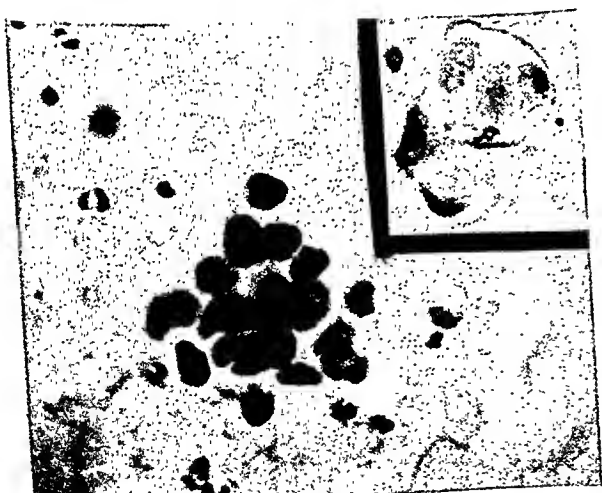
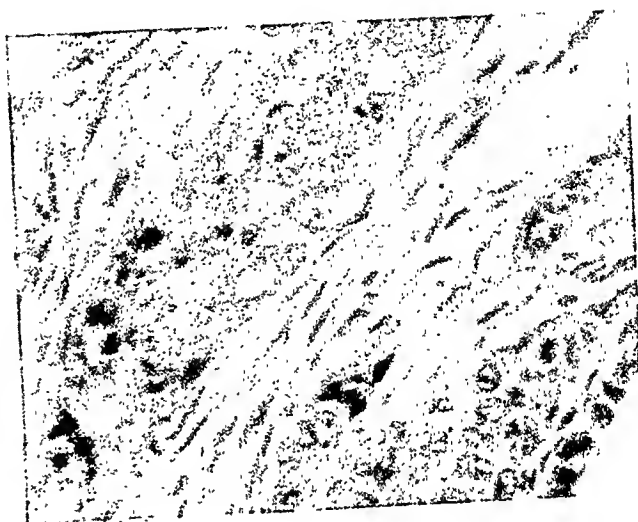
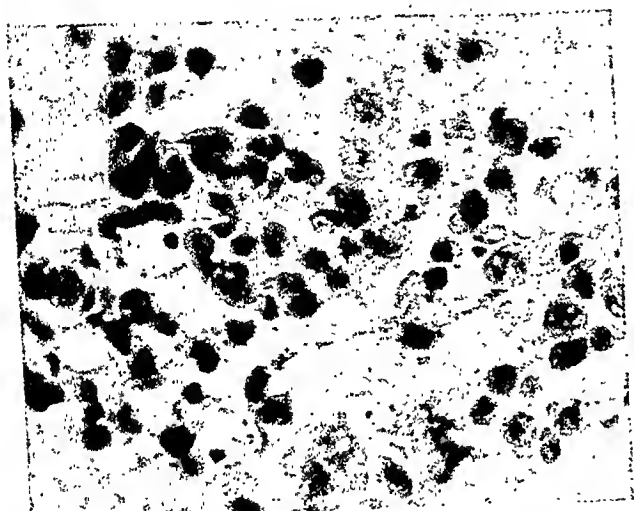
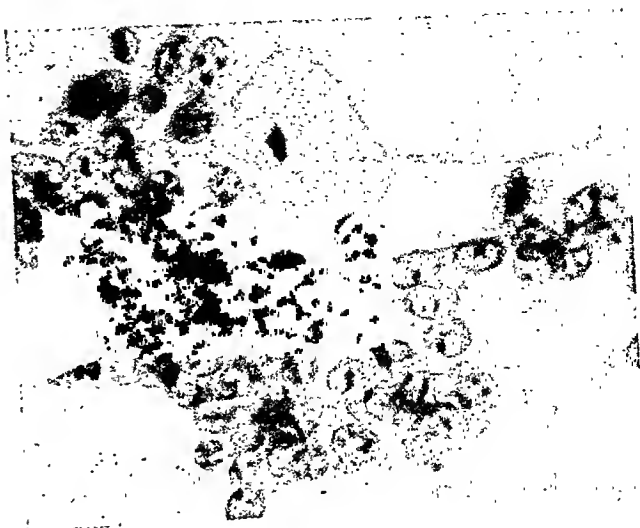
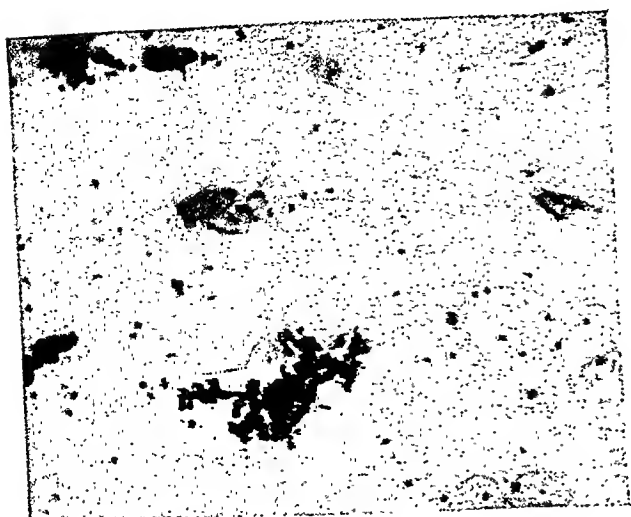


PLATE C

1. Cervical cytology smear in a case of fundal carcinoma. Note malignant-appearing endometrial cells found in the bloody mucus at the external os. (Low power.)
2. High power of 1 showing endometrial cells overlying a normal vaginal squamous cell.
3. Smear taken directly from surface of growth in same case at the time of operation. Observe the same type of cell found in the smear with the cytoplasm in a better state of preservation.
4. Tissue biopsy in same case showing infiltration of the uterine wall. There was also metastasis to the tubes.
5. Cluster of malignant-appearing cells in blood and secretion taken from external os in case of squamous carcinoma of cervix.
6. Same case showing cellular material aspirated from cervical secretions prepared by centrifuge technique. Note occasional mitotic figures.

cancer cells being spread widely through the field of mucus, blood, and pus as they are in the smears, the cellular elements were segregated into different strata on the basis of their respective specific gravities, so that most of the cancer cells were thrown together in a cluster (Plate B, 6). Thus it appeared that the centrifuge test had the following advantages over the smear:

1. It could be readily mailed.
2. The cancer cells were more quickly identified as they were thrown together by the centrifuge.
3. The laboratory work could be done in any pathology laboratory without specialized equipment.
4. Staining was simplified as ordinary hematoxylin and eosin was usually satisfactory for routine use, while the excellent trichrome strain of Papanicolaou may be used for greater nuclear definition in questionable cases.

It would appear that the field of cytology opens a broader horizon in early cancer diagnosis in gynecology. Only time will decide its true value by further trial and practice. In the meantime, it presents a challenge to public health authorities to put it to the test in their never-ceasing efforts to curb this dread disease.

TABLE I. DISTRIBUTION OF LESIONS IN 100 CASES

Cervix	81
Corpus	13
Vagina	3
Vulva and clitoris	3

TABLE II. RESULTS

Total number of cases investigated (Patients of cancer age or with cancer signs or symptoms)	580
Smears diagnosed positive for cancer	105
Smears diagnosed negative for cancer	475
Number with positive smears having positive biopsy	96
Number with positive or suspicious smears having negative biopsy	9
Percentage of error—8	
Number with negative smears having positive biopsy	4
Percentage of error—4	

Summary and Conclusions

This report consists of an analysis of one hundred cases of genital malignancy studied in the Gynecologic Cytology Division of the Royal Victoria Hospital. Photomicrographs of representative cases are presented. Of the one hundred cases giving a tissue diagnosis of malignancy, the cytology smears showed an average error of 6 per cent.

Smears taken routinely from the external cervical os have been found more reliable in diagnosis than vaginal smears.

An interesting observation is that many of the cases of malignancy in the postmenopausal age group show evidence of associated estrogenic activity.

The smear technique has been shown to be of value in detecting cancer at an early stage. It has proved helpful too in benign cases simulating malignancy clinically. Negative cell smears in such cases have been proved correct by biopsy. The method has also been found to be of value in assessing radiation therapy.

A new technique, the centrifuge cytology technique, has been presented briefly with illustrations.

This series of one hundred cases of genital malignancy are from the private and public services of the following staff members of the Royal Victoria Hospital: W. W. Chipman, J. R. Fraser, W. A. G. Bauld, P. J. Kearns, I. Y. Patriek, G. B. Maughan, N. W. Philpott, G. C. Melhado, J. S. Henry, W. R. Foote, and J. E. Ayre.

The author wishes to express sincere appreciation to the members of the staff for their kind cooperation. To Dr. W. A. G. Bauld and Professor N. W. Philpott, particular thanks is rendered for helpful advice and assistance in the preparation of this work. Miss Evelyn Dakin, Chief Technician in the Gynecologic Cytology Department, has contributed a great deal toward the success of this work in developing a fine staining technique. To H. S. Hayden, F.R.P.S., belongs the credit for the excellent photomicrography.

Grateful acknowledgment is made to the Ortho Research Foundation of Luiden, N. J., for generous assistance enabling publication of colored plate.

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1414 DRUMMOND STREET

Discussion

DR. McARTHUR.—Dr. Ayre and his associates certainly draw a hearty word of commendation for the meticulous way in which they have presented this work to us. I am sure from Dr. Ayre's comprehensive description, that this is not work that can be carried on by an amateur. It is of great value in the early diagnosis of cancer. I believe, however, that Dr. Ayre will agree that at the present time diagnostic curettage must still remain the sine qua non of investigation of the vaginal tract. I would ask Dr. Ayre if he knows of any studies on granulosa-cell tumors and results that they produce in the endometrium.

DR. SCOTT.—I would like to ask Dr. Ayre whether, in the course of his investigations, he has been able to diagnose cancer of the ovary or of the tubes. The early diagnosis of both of these conditions is very difficult, and any method that may assist us would be of the greatest value. It would seem probable that a cytological smear might occasionally reveal these conditions.

DR. HENDERSON.—I would like to add my commendations to Dr. Ayre on this presentation, which must have entailed hours of tiring work in the laboratory. He cannot be too highly complimented on the excellence of the technique.

Vaginal smear and cervical aspiration will establish the diagnosis in a very high percentage of cases, probably 98 per cent of the cases. When it comes to the diagnosis of adenocarcinoma of the uterus, even with cervical aspiration we have met considerable failure. It would be very valuable, of course, if a curettage could be avoided, and aspiration could be taken in the office. That has not been our experience, but our experience has been limited. I think it would be unfortunate if we got the idea that it is destined to replace other methods of early diagnosis, although cancer cells undoubtedly can be recovered in advanced carcinoma. I do not see where the early diagnosis is assisted by the taking of a vaginal smear. It would

be unfortunate if a patient received a negative report from such a smear, only to find later that carcinoma existed. I think the patient would be better treated by diagnostic curettage.

DR. COSBIE.—Has Dr. Ayre had any experience with paracentesis in the diagnosis of cancer?

I think Dr. Ayre's method of centrifuging the cellular material is a real contribution to this study.

DR. BAULD.—All cases have been checked before being treated. No cases have been treated on the smear alone. I believe that this smear has come to the stage where it can be summarized as follows:

1. Checkup clinic. The time is not far away, we hope, when everyone will demand a yearly or bi-yearly checkup by vaginal smear for early cancer.
2. It is of great value preoperatively, following operation, or to make it possible for a patient to have only one operation instead of two.
3. Checking the cures. Those that show evidence of recurrence. A great advantage is the development of the centrifuging method.

DR. ROBERTSON.—We have been attempting to popularize the smear technique at Queen's.

In speaking of the public health aspect of this, I think it is very important. I hope that the time is not far distant when a smear will be taken every two years to check for early cancer which would not be diagnosed otherwise, and it will take women to the doctor for frequent examination.

Authorities in Ontario have recognized the importance of this method by making grants for furthering this work.

We are trying to popularize a method of taking smears from the breast, especially in those cases where we might suspect cancer, or, at least, a mastitis. This work has not gone very far, but it is interesting to see how far the investigation will go.

DR. AYRE (Closing).—In response to Dr. Scott's question of whether we have studied smears from cases of granulosa-cell tumors of the ovary, I can only say that we have not had positive evidence of this finding. We did have one case of a 70-year-old woman showing postmenopausal bleeding associated with a tumor in one ovary. Vaginal smears in this case showed a high cornification level, indicating a rich estrogenic secretion. In addition, her curettage revealed a very hyperplastic endometrial pattern. This was a private case of Dr. John R. Fraser, and he indicated to me at the time that this was probably a granulosa-cell tumor of the ovary but felt that this could not be proved as a severe myocardial lesion definitely contraindicated major operative interference. Therefore, we never have had any positive verification that this was a granulosa-cell tumor, nor have we been fortunate enough to obtain smears from any proved case of a granulosa-cell tumor prior to operation.

In response to Dr. Scott's second question of whether we have been successful in diagnosing carcinoma of the Fallopian tube by the cytology method, again I must answer in the negative. Since starting the study of vaginal smears in our clinic three years ago, we have only encountered one case of carcinoma of the tube, and here the diagnosis was not made until after the operation had been performed. I have seen one case, however, a patient of Dr. Papanicolaou, where the cancer cells appeared in the smears from a malignancy arising in the tube.

Dr. Henderson has asked whether we did not still consider diagnostic curettage as the fundamental criterion upon which to base a diagnosis of endometrial carcinoma. I am in total agreement with Dr. Henderson on this score, as we have always maintained that the cytology tests must as yet be considered preliminary diagnostic measures to be confirmed by endometrial biopsy before any major therapy is undertaken. Even so, the cytology test still has an important role to play, as it provides an immediate accurate presumptive diagnosis.

Dr. Henderson has intimated that he felt that cancer cells could be picked up in advanced carcinoma, but that the method was not so valuable in the diagnosis of early carcinoma. This has not been our experience. We have had a number of cases where the lesion was so small as to miss detection by the examining finger, the eye, and even 50 per cent of the surgical biopsies. Yet in these cases cytology smears taken from the external os revealed the telltale malignant cells. Indeed, we feel that this method has as its greatest contribution to cancer diagnosis the ability to render an accurate presumptive diagnosis so early in the disease that the clinical appearance of the lesion may be identical to that of an erosion.

Dr. Cosbie has asked whether we have succeeded in finding malignant cells from ascitic fluid by paracentesis in cases of ovarian carcinoma. We have had several cases of this sort where the specimen of fluid has been centrifuged, revealing large numbers of these malignant-appearing cells. I had intended to include the picture of one of these cases along with the present report, but failed to have it photographed in time.

With regard to Dr. Robertson's reference to the work of Dr. Papanicolaou in centrifuging the urine of patients suffering from carcinoma of the bladder, I have only recently become aware of this. He has not only made a major contribution in the field of cancer cytology, but he was the one who really made the prime discovery that the bizarre cells floating down in the secretions to the vagina were actually malignant cells.

CARCINOMA OF THE CERVIX AFTER SUPRAVAGINAL HYSTERECTOMY*

W. G. COSBIE, M.B. (TOR.), TORONTO, ONTARIO

(From the Department of Gynaecology, The University of Toronto, the Toronto General Hospital, and the Ontario Institute of Radiotherapy)

IN THE sixteen years from 1929 to 1944, inclusive, 890 public ward patients have received their primary treatment for carcinoma of the cervix of the uterus at the Institute. Sixty-two of these patients had had supravaginal hysterectomy prior to admission, and they may be divided into two classes, depending on whether the carcinoma was diagnosed within three years of the time of operation or after a longer period of time. The first group is composed of patients believed to be suffering from carcinoma existing at the time of operation, and they will be referred to as suffering from coincident carcinoma, and the second group will be referred to as those suffering from carcinoma of the stump of the cervix. The division is made at the three- rather than the usual two-year period because the histories of several patients suggested that this would be more accurate. There may be a tendency to question whether some of the patients may not have had carcinoma of the body of the uterus undiagnosed at the time of the supravaginal hysterectomy. So far as possible, this has been checked by a review of the histories. It was noted that five of the 62 patients had adenocarcinoma, and this incidence is in keeping with a diagnosis of carcinoma of the cervix.

Twenty-four patients had carcinoma coincident with supravaginal hysterectomy. Failure to investigate the cause of vaginal bleeding accounted for the performance of practically all of these operations. The surgeons who performed them were probably for the most part followers of the ancient Alexandrian School of the Empirics whose doctrine was that in medicine reasoning was useless and experience alone was necessary. Minds such as theirs think only in terms of signs and symptoms and give no thought to underlying pathology. Curettage and biopsy are forgotten in the alacrity with which they grasp the scalpel, and their reaction to uterine hemorrhage is as rational as the cry of the old Queen of Hearts in *Alice in Wonderland*, "off with his head."

Twenty patients came for treatment within a year of the operation, and fifteen of these had very advanced tumors which could not have been missed had a preoperative vaginal examination been made. Ten had postmenopausal bleeding, and even this generally accepted danger signal was neglected. The fact that three of these patients had fibroids only emphasizes the sound diagnostic principle that the most obvious pathology is not necessarily the cause of a symptom.

Five patients were said to have had total hysterectomy. These represented incomplete preoperative investigation and a lack of surgical skill, and also an ignorance of the principles governing the surgical irradiation of carcinoma of

*Presented at the First Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, held in Montreal, Quebec, June 15, 1945.

the cervix. All the patients when admitted to the Institute had massive lesions at the vault of the vagina embodying the remains of the cervix. One of them brought a letter stating that the operation had been performed for the relief of the symptoms as the patient could not afford the cost of irradiation therapy. Another had commenced a course of high voltage therapy in another city and almost immediately moved to Toronto and came under the care of a surgeon who performed supravaginal hysterectomy, although he had been informed of a positive pathologic diagnosis of carcinoma of the cervix.

Lest it be felt that this study has been undertaken with criticism "lynx-eyed to our neighbours and moles to ourselves," the histories of three women are presented who were operated upon in the gynecologic wards of the Toronto General Hospital. These exemplify the pitfalls which constantly beset the feet of the unwary.

CASE 1.—Mrs. R. S. was first seen in 1932. She was 51 years of age and had had the menopause five years before. She was suffering from pelvic inflammation, and positive Neisserian smears were obtained from the cervix and the urethra. She had a brownish purulent discharge but no actual bleeding. The cervix was very unhealthy, and three times it was noted on her hospital record that a biopsy was advisable. This was never done, however, and about six months later she was operated upon for the removal of painful adnexal masses. Total hysterectomy was being performed when the uterus tore away at the isthmus, exposing massive carcinoma of the endocervix invading the proximal parametrium. This tumor fortunately was highly radiosensitive and, in spite of treatment which might be considered inadequate, she is alive and well today after a period of thirteen years.

CASE 2.—Mrs. W. M., aged 39 years, came in 1934 with a history of irregular vaginal bleeding of nine months' duration. Prior to admission, a diagnosis of adenocarcinoma had been made on biopsy from some tissue which was projecting from the cervical canal. Pre-operative examination did not show any visible sign of carcinoma of the cervix, and curettage suggested that the tumor was involving the body of the uterus. Total hysterectomy was undertaken but could not be completed because of an endocervical carcinoma extending extra-peritoneally, and the adnexa on one side fixed to the malignant mass. This patient survived nine years after irradiation before dying of recurrent carcinoma.

CASE 3.—Mrs. I. M., aged 46 years, was seen first in 1940. She was almost exsanguinated from uterine hemorrhage, and the uterus contained several large fibroids. After repeated transfusion, a supravaginal hysterectomy was performed. No note was made with regard to the condition of the cervix preoperatively, but at the examination before discharge from the hospital it was noted that "the cervix is unhealthy and should have been cauterized prior to operation." This patient disappeared for three years and nine months and returned complaining of vaginal bleeding which she said had commenced within a few months of the operation. Examination showed a stage III carcinoma of the cervix. It is altogether likely that the tumor was present at the time of removal of the body of the uterus, and that this is an example of the slow rate of growth seen in some carcinomas of the cervix. This patient was treated by irradiation and is alive and free of disease at the present time.

Childbirth injury and the consequent development of chronic cervicitis has been so strongly emphasized in the etiology of carcinoma of the cervix that a nulliparous patient with such a tumor is regarded as almost an anomaly. It is interesting, therefore, to note nine nulliparous women in the group of 62 under consideration. This is a slightly higher incidence than might be expected, as the incidence of nulliparity for all patients with carcinoma of the cervix in our clinic has been approximately 10 per cent. It may be partly explained as a

feature of a group of patients, half of whom had uterine fibroids and, therefore, a low degree of fertility. The potential danger of the nulliparous cervix cannot be too strongly emphasized. It is probably true that no such thought crosses the mind of the average surgeon undertaking supravaginal hysterectomy, and even those whose judgment prompts a more frequent performance of total hysterectomy may adopt a too casual reaction to the virgin cervix. Our experience with a high incidence of nulliparous patients with carcinoma of the cervix after supravaginal hysterectomy has been repeatedly noted in the literature. Meigs¹ reported 23 per cent, Pemberton,² 25 per cent, and Watkins,³ 28 per cent of nulliparous women in a similar series.

A 90 per cent incidence of parity should not be interpreted as representing the relative likelihood of carcinoma developing after childbirth as compared with the nulliparous state. It must be remembered that in the average cancer age group, namely, the decade about the forty-eighth year, approximately 90 per cent of women are married and only 10 per cent are unmarried. Naturally, all married women are not necessarily parous, but so far as can be ascertained, the incidence of infertility is about 10 per cent.^{4, 5} Therefore, it may be concluded that carcinoma of the cervix occurs only about twice as frequently in parous as in nulliparous women.

There is another phase of the question to consider. Cancer prevention clinics stress the importance of treating "precancerous lesions,"⁶ and the decision between supravaginal hysterectomy and total hysterectomy often rests on the appearance of the cervix. Martzloff⁷ has stated that he doubts that one can foretell from the appearance of the cervix whether a benign inflammatory process is more likely to develop carcinoma than a normal-appearing cervix. All the early carcinomas seen by him occurred in relatively normal-appearing cervices. It is possible that a common fault in medical records has maintained confusion on this point, namely, the tendency to describe a malignant lesion in detail with little reference being made to the tissue in which it has developed. A great danger of an unhealthy cervix is that it may mask the presence of early carcinoma. Careful biopsy is often the only basis of diagnosis between benign inflammation and malignant disease. Chronic cervicitis is so common in women who have borne children that it would be unusual not to expect carcinoma to develop in association with it. A review of the gross appearance of the cervix in stage I carcinoma in our clinic shows that about half the tumors developed in cervices apparently otherwise healthy.

Many advocates of total hysterectomy stress the importance of the persistence of troublesome vaginal discharge from the residual cervix after supravaginal hysterectomy and suggest that chronic cervicitis not infrequently develops after the removal of the body of the uterus. This has not been the experience of myself or my colleagues at the Toronto General Hospital. As a matter of fact, in the group of 38 patients who suffered from carcinoma of the stump of the cervix, 24 were free of vaginal discharge following supravaginal hysterectomy and did not have any symptoms referable to the cervix until shortly before the carcinoma was diagnosed. Twenty patients did not develop symptoms of carcinoma until at least ten years had elapsed after the operation.

Seventeen patients had had double salpingo-oophorectomy at the time of hysterectomy. It would seem that these observations suggest the likelihood of cervical atrophy after supravaginal hysterectomy rather than the persistence or development of chronic cervicitis.

It is impossible to estimate accurately the incidence of carcinoma of the stump of the cervix as a postoperative complication. In this study, 10 of the 38 patients with carcinoma of the stump of the cervix did not develop symptoms of the tumor until fifteen years or more had elapsed after the operation, the longest interval being thirty-six years. Seven of the cases of cervical stump carcinoma had been operated upon on our gynecologic wards. The interval between the operation and the diagnosis of carcinoma varied from four to fifteen years, and one patient had been operated upon in 1916. It is obvious, therefore, that no postoperative follow-up system can be maintained long enough to answer the question with any degree of accuracy. Viewed from another angle, it is significant that cervical stump carcinoma constitutes 4.2 per cent of all cervical carcinoma receiving primary treatment on the public wards at the Institute.

Prevention is always better than a cure, and total hysterectomy would certainly have prevented the development of carcinoma in these 38 patients. The attitude of the gynecologic service at the Toronto General Hospital toward the operation of hysterectomy has always been extremely conservative. Prior to 1938, less than 10 per cent of the hysterectomies performed were total hysterectomies. Since then the incidence has risen to approximately 25 per cent. Our experience is that most patients who are to be considered bad surgical risks will be subjected to supravaginal hysterectomy. This means women with organic disease or who are extremely fat, those with extensive inflammatory disease or endometriosis, and some cases of fibroids where the location of the tumor makes the approach to the vault of the vagina very difficult. Therefore, an operative mortality rate during the last eight years of 1 per cent for total hysterectomy and 0.9 per cent for supravaginal hysterectomy represents a careful choice of cases for the major procedure. It is to be realized also that most of the deaths were due to the conditions for which the operations were undertaken, rather than to the inherent risk of the operation. Frequently, hysterectomy has been merely part of a procedure to irradiate extrauterine pelvic disease.

A review of the history of the cases of carcinoma of the cervical stump suggests that many more total hysterectomies might have been performed without increasing materially the operative risk to the patient. Twenty-three patients were operated upon for uterine bleeding, and 15 of these had uterine fibroids. Only eight operations were performed for pelvic inflammatory disease. It should be realized, however, that in this country, apart from the larger centers and better hospitals, the vast majority of hysterectomies are not performed by trained gynecologists. Supravaginal hysterectomy is the operation undertaken by the occasional operator and is applied by him to every case where removal of the uterus is indicated.

The practice of combining cauterization of the cervix with supravaginal hysterectomy has had extensive use at the Toronto General Hospital. In 1937

this was done in 44 per cent of the subtotal hysterectomies, but in the last three years with the greater use of total hysterectomy the incidence has dropped to 15 per cent. Apart from the belief that cauterization was a satisfactory method of treating chronic cervicitis, it was felt by some that it was of value as a means of cancer prophylaxis. While it is true that deep cautery destruction of the cervix lowers the incidence of carcinoma, this⁸ does not apply to anything like the same extent to the lighter cauterization associated with supravaginal hysterectomy. Six patients who developed stump carcinoma had cervical cauterization at the time of the operation. Cervical cauterization presents another danger which is exemplified by three women who had coincident carcinoma. They were subjected to repeated cauterization postoperatively on the mistaken assumption that the unhealthy appearance of the cervix was due to chronic cervicitis, while time alone proved the presence of malignant disease.

A group of only 62 patients treated over a long period of time and by various routines of radiotherapy does not constitute a satisfactory basis for a comparison of the results, but may permit some general observations.

TABLE I. THE SURVIVAL RATE OF THIRTY-EIGHT PATIENTS WITH STUMP CARCINOMA

STAGE	1 YEAR	3 YEARS	5 YEARS
I	8 of 8	6 of 6	5 of 5
II	9 of 14*	4 of 12	1 of 6*
III	10 of 13	6 of 11	3 of 8
IV	0 of 3	0 of 3	0 of 1
Per cent survival	70	50	45
Incidence of stage I carcinoma—21%			

*Including death from extraneous disease.

TABLE II. THE SURVIVAL RATE OF TWENTY-THREE PATIENTS WITH COINCIDENT CARCINOMA

STAGE	1 YEAR	3 YEARS	5 YEARS
I	4 of 4	2 of 2	1 of 1
II	2 of 3	0 of 3	0 of 1
III	6 of 9	3 of 6	1 of 3
IV	3 of 7	1 of 6	1 of 5
Per cent survival	58	35	30
Incidence of stage I carcinoma—17%			

*One patient not included as treated during current year.

The results of treatment of the patients suffering from carcinoma of the stump of the cervix have been better than the results of the treatment of the patients with carcinoma of the cervix when the body of the uterus was present. The three-year survival rates were 50 per cent and 39 per cent, respectively, and the five-year rates were 45 per cent and 30 per cent, respectively.

It is altogether likely that postoperative fibrosis about the vault of the vagina and the remains of the cervix interfered with the lymphatic drainage, and so reduced the tendency to deep pelvic gland involvement. A decreased blood supply and the atrophy of the tissues consequent on the removal of the ovaries which often accompanied supravaginal hysterectomy may also contribute to a slow rate of growth. It is certain that the high incidence of stage I carcinoma, namely, 21 per cent in stump carcinoma and 17 per cent in coincident

carcinoma, had a favorable effect on the survival rates as all 12 patients who had stage I carcinoma are alive at the present time.

A favorable age distribution also contributed to the good results. The ages ranged from 35 to 68 years, and there were no very young patients. Our experience has been that these always present a very poor prognosis. The patients under 30 years of age who we have treated have shown a five-year survival rate of only 12 per cent, against 30 per cent for the whole group of patients treated.

The results of the treatment of coincident carcinoma have been unexpectedly good. It is rather likely that the extent of the tumor may have been overestimated in some cases as a result of mistaking postoperative thickening about the vault of the vagina for malignant infiltration. A table has been prepared to show the great difference in the results of irradiation treatment between the patients who were treated within a year after the operation and those who were treated after considerable time had elapsed. In these latter cases the estimation of the extent of the disease was undoubtedly more accurate. Delay in instituting treatment has always been disastrous.

TABLE III. THE EFFECT OF EARLY OR LATE TREATMENT ON THE SURVIVAL RATE IN COINCIDENT CARCINOMA

STAGE	RECEIVED TREATMENT	SURVIVAL RATE		
		1 YEAR	3 YEARS	5 YEARS
I	Under 1 year	4 of 4	2 of 2	1 of 1
	Over 1 year	--	--	--
II	Under 1 year	--	--	--
	Over 1 year	2 of 3	0 of 3	0 of 1
III	Under 1 year	4 of 6	3 of 4	1 of 2
	Over 1 year	2 of 3	0 of 2	0 of 1
IV	Under 1 year	3 of 4	1 of 4	1 of 3
	Over 1 year	0 of 3	0 of 2	0 of 2

In order to obtain a maximum rate of cure in the treatment of malignant disease by irradiation therapy, it is often necessary to carry the treatment to the limit of toleration of the normal tissue which lies within the range of the irradiation. It is to be expected that patients who have considerable distortion of pelvic anatomy as a result of removal of the body of the uterus would be more liable to injury to adjacent structures. Postirradiation fistula has only occurred once in this series of patients and then was due to an extensive tumor finally breaking down to form both vesicovaginal and rectovaginal fistulas. It has, however, been our experience that postirradiation proctitis, cystitis, and enteritis have developed more frequently than has been the case in the whole group of patients with carcinoma of the cervix.

Conclusions

1. Uterine hemorrhage is a symptom of major importance, and the recognition of its cause is essential to avoid the paradox of supravaginal hysterectomy for carcinoma of the cervix.

2. The incidence of carcinoma of the stump of the cervix justifies advocating the more frequent performance of total hysterectomy.

3. The effectiveness of postoperative irradiation therapy depends on its prompt application.

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Discussion

DR. A. D. CAMPBELL.—There is a moral in Dr. Cosbie's paper. In fact, Dr. Cosbie makes a plea for gynecologic cases to be more thoroughly examined and treated by trained gynecologists rather than by those who are self-styled or those so-called surgeons who regard themselves as authorities on all aspects of operative gynecology.

I have long since been convinced that the cervix should not be divorced from the fundus of the uterus, and that supracervical hysterectomy should better be treated as incomplete hysterectomy. The neglected cervix is heir to all lesions peculiar to the cervix.

In certain instances, the operation of abdominal hysterectomy is incidental to the proper surgical treatment of a perforated diverticulitis involving the adnexa. Here the uterus and its involved adnexa must, of necessity, be removed in order to establish adequate treatment of the abscess. Similarly, when a carcinomatous growth of the ovary or ovaries filling the pelvis threatens complete obstruction of the sigmoid, a permanent colostomy may be averted by removing the uterus with the associated carcinomatous mass. Such factors as these, therefore, vicerate statistics on hysterectomy.

In reviewing hysterectomies in The Montreal General Hospital since 1926, it is interesting to observe the general trend toward total hysterectomy. Prior to 1934, only 18 per cent of hysterectomies were complete. From the years 1935 to 1944, the swing toward complete hysterectomy gradually rose to over 65 per cent. In the entire series of over 3,300 hysterectomies, the mortality during this twenty-year period dropped from 2.64 per cent to 1 per cent. If vaginal hysterectomies were included, total or (complete) hysterectomies would have reached 90 per cent. However, in the vast majority of vaginal hysterectomies, removal of the uterus was simply incidental to the proper reconstruction of the badly damaged birth canal.

In 1940, we devised a technique whereby the deperitonealized pelvis, after complete extirpation of the pelvic organs for endometriosis or pelvic inflammatory disease, could be peritonealized. By this marsupialization of the infected or damaged pelvic basin, the morbidity was materially reduced. It is worthy of note that none of these cases was given sulfonamides, nor did any suffer postoperative discomfort from distension.

In addition to the meticulous peritonealizing, adequate drainage must be established through the vaginal vault.

In conclusion, may I again emphasize that, while many surgeons are capable of removing the supracervical portion of the uterus, it is equally important that they should recognize an unhealthy cervix before submitting a patient to an incomplete hysterectomy.

DR. ELEANOR PERCIVAL.—At The Montreal General Hospital we found 19 cases of this type out of 468 cases of cancer of the cervix. Of these 19 cases, there were stumps that were left following cancer of the fundus. Cancer of the fundus was not diagnosed preoperatively, and the cervix was left behind. Of these 16 remaining patients, only four were nulliparous, and it is curious that these four patients who developed carcinoma of the cervical stump are all dead. The number is too small to be significant; it is only of interest. Eighteen lesions were epidermoid, one adenocarcinoma. All were treated with radium. Of the 19 patients, 12 are still alive, but these are cases treated up to 1943.

GESTATIONAL NEURONITIS*

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GESTATIONAL neuronitis is not one of the common complications of pregnancy but, nonetheless, is an interesting and important one and, from an etiological standpoint, may in the future hold some interesting possibilities in relation to other toxemias of pregnancy. I would introduce the subject by giving you briefly the histories of two patients, the first of whom was my introduction to the subject of gestational neuronitis or, as it is variously called, toxic neuronitis or polyneuritis of pregnancy.

CASE 1.—Mrs. E. P., a primipara, aged 25 years. This patient was first seen in August, 1933, with a history of three months' amenorrhea. Menstruation had started at 13 years and had been regular and normal up to 19 years of age, but since then had occurred only three or four times a year. Her weight had increased in that same period from 140 to 211 pounds. Apart from this, her general examination was negative, and pelvic examination revealed no signs of pregnancy. Her basal metabolic rate was 14 per cent. She was given thyroid and a reducing diet. She was next seen on October 15, still with amenorrhea, but now complaining of nausea and vomiting every day; on examination, she was found pregnant. The nausea and vomiting persisted and increased in spite of treatment at home, and, on November 1, she was admitted to the hospital unable to retain anything by mouth. With intravenous and rectal glucose and sedatives, etc., the vomiting promptly ceased and, in a week's time, she was able to take a reasonably substantial diet, but continued to complain of being generally weak and tired. On November 15, she complained of pains in her legs and feet, and each day this complaint became more persistent and more marked, together with an increasing weakness in the legs and difficulty in standing. At the end of the week, this difficulty was quite marked and there was some weakness in the hands, with difficulty in picking up objects. The reflexes were hyperactive and there was marked pain on deep pressure over the muscles of the legs. On November 24, there was a paralysis of both feet with loss of the ankle jerks, and she could raise her legs with difficulty. Other examination was negative, except for a persistent tachycardia, the pulse being 120. The blood pressure was 115/70. The urine was negative and there was no abnormal blood chemistry. That evening there was a slight blurring of vision. All day she had been very confused in her mind, at times not remembering where she was, and at other times worrying for fear she had done something to injure her baby. In twenty-four hours the paralysis had rapidly extended to involve both legs completely, the abdominal muscles, bladder, and rectum. There was complete loss of vision, and examination of the eye grounds showed edema of the discs and massive subretinal hemorrhages. There was some lateral nystagmus. The tachycardia had increased, the pulse being 140. The blood pressure was 120/70. Catheter urine showed a plus 2 albumin and plus 3 red blood cells.

At this point, a therapeutic abortion was done under spinal anesthesia, and a pregnancy of approximately 2½ to 3 months was removed. Following the termination of the pregnancy, there was no further progression of symptoms. The urine cleared in two days. The pulse rate returned to normal in three weeks, by which time the mental confusion had disappeared, and her vision had greatly improved, eventually returning to normal. The paralysis, however, was slow in recovering; it was eighteen months before she walked normally without the use of canes. In 1938 this patient became pregnant again and went to term without incident.

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CASE 2.—Mrs. E. H., a primipara, aged 25 years, was seen in consultation in the hospital in January, 1941. She had been admitted to the hospital in December with persistent vomiting, which cleared up readily with intravenous and rectal glucose, sedatives, etc.; and she had been sent home eating well. After a short interval, the vomiting recurred, gradually increasing in severity over a period of two weeks before her readmission on January 1, at which time she was 3 to 3½ months pregnant. Her response to treatment at this time was not complete, and she continued to vomit once or twice a day in spite of taking a fair amount of nourishment on a high protein and carbohydrate diet with fruit juices and vitamins. Her condition remained at this stage until January 25, when she began to complain of pains in her legs and feet and numbness and tingling in her hands and arms. At this time she was given additional vitamin B in large doses intramuscularly. The pains in her legs increased in severity, and there was marked pain on deep pressure over the muscles and progressive weakness of the legs. She had a persistent tachycardia, with some enlargement of the heart and soft blowing murmurs at the apex. Her blood pressure was 120/70; and she complained of some dyspnea. On January 28 there was a paralysis of both feet, and the legs could be raised from the bed only with great difficulty. There was some blurring of vision. On January 29, the paralysis involved both legs, and there was loss of bladder and rectal control. There was weakness of the abdominal muscles and difficulty in sitting up. In the next twelve hours the paralysis quickly progressed to involve the abdominal muscles and the diaphragm. Breathing was very labored, the pulse rate was increased to 150, the blood pressure was 126/70, and the cardiac murmurs more pronounced. There was no change in the blood chemistry, but the urine which had been normal now showed a plus 3 albumin and plus 4 red blood cells. The spinal fluid was negative.

A hysterotomy was done now under spinal anesthesia, and a 4 to 4½ months' pregnancy removed. Following the termination of the pregnancy, there was no further progression of symptoms. The vomiting stopped, the urine cleared in a few days, the myocardial symptoms rapidly improved, as did the vision. The neurological symptoms, as in the other case, were slow in improving and in all took a period of sixteen months.

Comment

Etiology.—This condition was first noted in the literature in 1854, in an article by Churchill of Dublin. He gave as the causes of this disease, anemia, uremia, rheumatism, and hysteria. For many years, hysteria was the favored etiological factor. Moebius, in 1887, was among the first to suggest a theory of autointoxication, stating that some morbid condition of the blood of the pregnant woman was the cause of the paralysis. Whitfield first noted the occurrence of paralysis following or associated with the vomiting of pregnancy, and published in the *Journal-Lancet* in 1889 an article entitled, "Peripheral Neuritis Due to Vomiting of Pregnancy," and included the report of such a case. Tuillant, in 1890, also noted the occurrence of paralysis following vomiting of pregnancy and suggested that it was due to lack of nourishment. Occasional cases were reported by various authors through the years, and, in 1932, Berkwitz and Lufkin reviewed 500 cases in the literature of paralysis occurring in pregnancy, and from these collected 48 undoubted cases of toxie neuronitis. To this they added four patients of their own, three of whom had died and upon whom they had made complete autopsy and microscopic studies. Their conclusion was that, since this condition cleared up only with termination of the pregnancy or ended in the death of the patient, it was a true toxemia of pregnancy and so named it toxie neuronitis. This was the generally accepted theory of causation up to this time in this country and on the Continent.

It appears, however, that in Oriental countries where deficiency diseases are endemic, this condition had long been known as a complication of pregnancy, and as early as 1904 to 1905 beriberi and its association with pregnancy had been reported there. Theobald, in 1930, suggested that the neuritis of pregnancy was due to a vitamin B deficiency, the neuritic form of beriberi in Bangkok being twice as common in the pregnant woman as in the nonpregnant and that, furthermore, the symptoms of beriberi were indistinguishable from those of polyneuritis of pregnancy. Many authors in these countries thought that not only was the

polyneuritis of pregnancy a deficiency disease but that this was the etiological factor in the other toxemias of pregnancy, and reported clinical evidence to show that adequate prophylactic treatment greatly reduced the incidence of pre-eclampsia and eclampsia. Siddall advanced the theory, based on his observations of prenatal cases suffering from beriberi in China, that normal function of the pituitary gland depended on an adequate supply of vitamin B. He felt that in the pregnant woman a deficiency of vitamin B led to an overcompensation or malignant hyperfunction in the gland, resulting eventually in the production of the various symptoms of the toxemias of pregnancy.

The idea that toxic neuritis of pregnancy was due to a so-called toxin elaborated during the pregnancy was changing in the minds of some to the theory of a deficiency disease. Strauss and McDonald, in 1933, reported three cases cured by high protein and vitamin B diets plus iron and liver. They stated that "this was definitely a deficiency disease brought about by lowered food intake because of the vomiting of pregnancy, by decreased absorption due to the altered gastric secretory function which occurs in pregnancy, by depletion of the maternal organism from the increased demands of the fetus, and, also, that the clinical and pathologic examinations in neuritis of pregnancy were identical with those of beriberi. Later, in 1938, Strauss stated that toxic neuritis of pregnancy, alcoholic neuritis, diabetic, biliary, and gastrogenous polyneuritides, postinfectious polyneuritis, the Korsakoff syndrome, and other misleading names, have concealed the true diagnosis of vitamin B deficiency; that clinically and pathologically these polyneuritides are identical with beriberi and only differ in the mechanism by which they are brought about.

Subsequent clinical and laboratory investigations tend to strengthen the theory of a deficiency disease. Williams, Griffith, and Fralin studied the vitamin B₁ intake in a series of prenatal cases, and found that only 37.1 per cent had an adequate intake. Horwitz and Farley, in studies on blood serum, found 13 women in the 86 prenatal cases reported to be deficient in vitamin B₁. Of these 13 who were deficient, 10 developed neuritic symptoms during their subsequent prenatal period. Stahler estimated the amount of vitamin excreted in the urine after giving 10 mg. of thiamine intramuscularly daily for four days. Of the 40 mg. given, the nonpregnant woman excreted 46 per cent, the pregnant woman, 30 per cent, showing the increased requirement of the pregnant woman. He made the same estimation on a case of polyneuritis of pregnancy and the percentage excreted was 11, showing a marked increase in tissue demand.

Pathology.—In the pathology of this disease, the absence of gross anatomic change is in striking contrast to the severity of the disease clinically. The brain and cord and peripheral nerves appear grossly normal. The thoracic and abdominal viscera show nothing abnormal. Microscopic study shows slight cloudy swelling in the kidneys and liver. The peripheral nerves show degenerative changes in the anterior horn cells, particularly in the lumbar region, the changes consisting of loss of Nissl substance, swelling of the cells, eccentricity of the cell nuclei, and occasionally cell necrosis. Petechial hemorrhages are frequently present in the cord or brain or in both.

Autopsy reports on cases of gestational neuronitis are very few and far between. Berkwitz and Lufkin reported three of their own and six others collected from the literature. These have been added to, most recently by Bingham, McGoogan, and Jones, all of whose findings are very constant and all of which are identical with those changes occurring in vitamin B deficiency. Jones noted the absence in his case, and I have not found any mention in other reports of the typical hydropic degeneration of the myocardium or beriberi heart, which in beriberi is the chief cause of death.

Symptomatology and Clinical Course.—For a discussion of the symptomatology and clinical course of this disease, I have classified all cases under three types, namely: (1) mild, (2) severe, and (3) fulminating.

1. *Mild type:* Practically all cases of gestational neuronitis reported in the literature are of a severe type with greater or lesser degrees of paralysis developing at some time in the course of the disease. In this group of cases the symptoms are: persistent tingling, or pain, or feeling of numbness in either feet or hands and often in both, and neuritic pains

in the arms and legs. These symptoms usually appear in the fourth month or later, and nearly always in a patient who has had a slightly more troublesome degree of nausea and vomiting in the early weeks. These symptoms, though persistent, are not progressive in character, and usually, after a varying length of time, regress or disappear, though I have seen them continue throughout the pregnancy. I would also place in this group a patient who, in addition to these symptoms, developed a unilateral ptosis of an eyelid, which cleared up only some months after delivery. I have noted two cases in the literature, one recently, of paralysis of isolated muscles, such as this case, both of which involved the serratus magnus.

2. *Severe type:* In this group the usual and almost invariable history is a moderately severe form of nausea and vomiting, requiring hospital treatment; this has responded well and the patient has been sent home. After a short period of remission, the vomiting recurs once or twice a day and the patient shows no interest in food at other times. This may go on for some weeks and she begins to complain of tingling pains in the feet and severe neuritic pains in the legs. Her complaints continue frequently and bitterly, until she is looked upon as a chronic complainer and often as a neurotic. To the pains in her legs is added a weakness which gradually interferes with walking and standing. Numbness and tingling pain in the hands may appear, with some incoordination and difficulty in picking up small objects. Often at this time, there are periods of forgetfulness and mental confusion which may add to the neurotic impression made upon others. Examination, however, shows a general weight loss, marked atrophy of the muscles which are soft and flabby, as well as weak. The knee and ankle jerks, which at first were hyperactive, are now diminished, and there is a tendency to foot drop and muscular contracture. The vomiting usually persists and there is a steady progression of symptoms, the neuritic and mental picture predominating. The muscular weakness extends to the abdomen and back, and the patient sits up only with great difficulty. Complete paralysis, with loss of the reflexes, starts in the toes and feet and gradually extends upward, involving the legs, the bladder and rectum, and abdominal muscles and diaphragm. On general examination, there is very often a dimming of vision progressing to a complete loss of sight, and examination of the eyes may show some nystagmus, the fundus showing some edema and optic neuritis with later subretinal hemorrhages. The chest is negative, the heart usually negative except for a persistent tachycardia, the blood pressure remaining normal. Laboratory examinations are consistently negative. The urine is clear, blood chemistry shows no changes, and the spinal fluid is normal. There is usually a moderate anemia. The paralysis progresses to involve the upper extremities, the muscles of deglutition, and finally the accessory muscles of respiration, and death occurs with the respiratory failure.

In some cases, the cardiovascular symptoms may appear before the paralysis and greatly predominate, with an increasing tachycardia, enlargement of the heart with increasingly evident murmurs, marked dyspnea, and a dependent or generalized edema, and death may be due to cardiovascular failure, as is usually the case in beriberi.

3. *Fulminating type:* This group of cases is typified by the two cases reported in this paper. The symptomatology is the same as in the second or severe type, but the development and progress of the disease is much more rapid and acute, and death may occur in two to four days from the onset of symptoms.

Prognosis and Treatment.—Mortality rates, as reported in the literature, run from 18 to 68 per cent, but most of these figures are on very small series of cases. McGoogan, in a more recent review, studied 130 cases collected from the literature, to which he added 15 of his own. In this group of 145 cases, there were 40 deaths, a mortality rate of 27.5 per cent. In 105 of these patients who received no vitamin B therapy, there were 37 deaths, or a rate of 35.2 per cent, while in the remaining 40 patients who received varying amounts and fractions of vitamin B, there were 3 deaths, or a mortality rate of 7.3 per cent. Even though this latter group included a higher percentage of mild cases, the mortality rate in this disease is high and it should be considered a serious complication of pregnancy.

Recovery, though slow, is usually complete. The cardiovascular and visual symptoms disappear quickly, the neurological symptoms slowly over a period of from three to eighteen months. A few cases are reported with permanent paralysis resulting.

In the treatment, emphasis should be placed first upon prevention and, from the weight of evidence, this should take the form of more active treatment of the nausea and vomiting of the early weeks of pregnancy with large doses of vitamin B₁ and the other B fractions, together with iron and liver and a diet well fortified with vitamins throughout the remainder of the prenatal period. The estimated daily requirement of vitamin B₁ is from 300 to 500 international units, and during pregnancy this should be increased by five times. In the first or mild type of case, 50 mg. of vitamin B₁ should be given daily plus the other B fractions until symptoms disappear, and then carried on a good sustaining dose throughout. In the severe cases, 50 to 100 mg. of B₁ plus the other fractions should be given. Iron should be given, and dilute hydrochloric acid where indicated. Quite frequently, the degree of anemia will require transfusion. Strauss recommends parenteral injections of liver extract, not only to combat the anemia, but because the liver fraction is of benefit in the neuritic symptoms.

In studying the treatment of this disease in the severe type, it would seem in many cases that either the dosage of vitamin B₁, or of the other B fractions, or both, are entirely inadequate, and that much higher doses are required, or that the vitamin deficiency over too long a period has resulted in the establishment of some irreversible process which ends only with the termination of the pregnancy. In those cases of the severe type where there is steady progression of symptoms in spite of adequate treatment, and in the acute fulminating type, such as the two cases reported here, I would feel that, in the light of our present knowledge, the pregnancy should be terminated.

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Discussion

DR. NASH.—Unfortunately, for the purpose of this discussion I have had no experience with this rather distressing and rather unusual complication of pregnancy, unless one includes those cases that present the problem to a lesser degree. It seems to me that in the recognition of these early manifestations and in their proper treatment lies the prevention of the more serious complications. It does seem that one of the causes of this disease must be that the dosage of thiamine chloride has been hopelessly inadequate. The amount of 300 mg. daily would not be excessive. It seems, also, that it is exceedingly important to recognize as early as possible the more serious manifestations, such as persistent nausea and vomiting. These may well be a source of perplexity for several days until their severity forces treatment and the evidence of neuritis becomes more manifest. In those patients suffering from severe neuritis and vomiting of pregnancy, the treatment popularly employed is apt to aggravate this condition. For glucose transfusions will decrease the thiamine chloride in the system. It is only conjecture to assume that this condition is a toxic manifestation of pregnancy. I am aware of no evidence that would render it reasonable at the present time. Certain authorities, writing of this recently, have maintained that it is not necessary to interrupt pregnancy because of the existence of this condition. Dr. Agnew has told us that in the severe type the pregnancy should be interrupted in certain cases. On what does he base his opinion

that the pregnancy should be interrupted? Are there not many cases quoted where the disease has been adequately treated as successfully as by interruption of the pregnancy?

DR. MANN.—There seems to be some doubt about the reason and justification for terminating pregnancy in these cases. To me, it appears from the case reports that we are here dealing with two cases of unusual gravity that did not respond to any treatment available at the present time. The condition was rapidly progressive, and it would appear that termination of the pregnancy was the only measure that would save the lives of these patients.

DR. AGNEW (Closing).—As to this condition being a toxemia, no real evidence has ever been produced in regard to any of the toxemias of pregnancy. As I tried to outline the evolution of the etiology of this disease, it was considered one of the toxemias of pregnancy, but with the passing years an increasing amount of evidence has been given that this is a deficiency disease. Dr. Mann has answered many of the points for me. The other point on which I would like to clear up any doubt is regarding the termination of pregnancy. In those severe cases where, in spite of every adequate treatment, the condition is slowly progressive over weeks or months to the dangerous stage, I feel that in the light of our present knowledge the pregnancy should be terminated. In the fulminating type one might have only a matter of hours or, at the most, days. In spite of certain statistics, and, with full respect for those who are very much opposed to the termination of pregnancy, I believe that in a few cases termination is the method of choice.

SPINAL ANESTHESIA IN VAGINAL DELIVERY*

A Report of 1,547 Cases

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A REPORT of 1,547 obstetric patients is presented, in whom small doses of spinal anesthesia were used for vaginal delivery at the Mount Hamilton Hospital. This covers a ten-year period from Jan. 1, 1935, to Dec. 31, 1944. During this period 101 cesarean sections were performed at the same hospital, as well as several hundred vaginal deliveries at Casa Maria and the Mountain Sanatorium, both of Hamilton, under spinal anesthesia; none of these is included in this report.

There is a widespread feeling among obstetricians and others that spinal anesthesia has special dangers to the pregnant woman, this opinion being reflected in the teaching of our medical schools. In view of the increasing use of intradural block for general and gynecologic surgery, and particularly for cesarean sections, the authors feel that our series has become large enough to justify a report of our experience in vaginal deliveries using small doses of novocain. Although the authors have no wish to "sell" this procedure to the medical profession, it is our desire to present an accurate picture of our results, including fetal and maternal mortality, difficulties, dangers, and possible advantages. It is our belief that there is a useful place in obstetrics for this method of delivery anesthesia and that the dangers in its use have been very much exaggerated.

One of us (R. T. W.) had the opportunity to be on the Resident Staff of the Margaret Hague Maternity Hospital, Jersey City, in 1932. At that time about 5,000 deliveries were done each year, spinal anesthesia being almost a routine. He confesses that he had all the usual prejudices against subarachnoid block and expected to leave that very active institution with those prejudices confirmed by actual experience of the difficulties and dangers. To his surprise he found himself converted to its use.

The development of spinal anesthesia in obstetrics in Hamilton has been much influenced by this fact, but no effort was made to promote its use. To employ a procedure not accepted by the profession at large would incur justifiable criticism in the event of a catastrophe. In spite of this, there has been a remarkable increase in the number and percentage of patients delivered by this means (Table I). In 1935 only two patients, or 0.02 per cent of the total deliveries, had spinal anesthesia, whereas last year, of 3,410 cases there was nearly 22 per cent. Up to 1940 only one doctor at the Mount Hamilton Hospital was using spinal anesthesia for vaginal delivery, while in 1944 that method was employed by twenty-three physicians.

*Presented at the First Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, held in Montreal, Quebec, June 15, 1945.

TABLE I

	TOTAL DELIVERIES	SPINAL DELIVERIES	SPINAL PER CENT	NUMBER OF DOCTORS
1935	779	2	0.02	1
1936	826	10	1.2	2
1937	923	8	0.86	1
1938	1,128	19	1.7	1
1939	1,630	32	1.9	1
1940	1,726	53	3.1	4
1941	2,264	71	3.1	5
1942	2,929	204	7.0	10
1943	3,348	401	11.9	18
1944	3,410	747	21.9	23
Total	18,963	1,547	8.1	66

The technique is essentially the same as for intradural block for general surgery, except that sterile gloves are used without previous scrubbing. The patient is curled up in a comfortable lateral position, usually without being held by a nurse or assistant. The length of time required for painting the back with an antiseptic solution and for the administration of the anesthetic agent is rarely more than two or three minutes. The relief of pain occurs with dramatic rapidity; even with violent two-minute pains it is unusual for the patient to experience more than one uncomfortable contraction following the injection. The patient is placed in lithotomy position, in stirrups, and prepared for delivery while the obstetrician is scrubbing.

Novocain crystals dissolved in about 2 c.c. of spinal fluid is the anesthetic of choice, injected into the third or fourth lumbar interspace without barbotage. The small dose employed, 50 mg., is sufficient to give a painless delivery, but does not materially decrease uterine contractions. The duration of anesthesia, with good perineal relaxation, is about one hour, allowing ample time for a forceps delivery and the repair of an episiotomy. It has been our practice to use outlet forceps and episiotomy in the majority of our cases, regardless of the type of anesthetic employed. That procedure is usually necessary when spinal anesthesia is used, as the involuntary expulsive efforts of the patient have been eliminated. In cases requiring increased uterine relaxation, such as internal podalic version, some general anesthetic may be necessary. We often employ spinal in such patients, however, because the amount of supplementary anesthetic is very small and is administered only for the actual intrauterine manipulation.

One of the objections often mentioned to the use of spinal anesthesia for delivery is the difficulty of obtaining a satisfactory tap. In our experience this is more imaginary than real. With a reasonable knowledge of the anatomy involved and a systemic approach, the inability to inject the solution into the spinal canal is a comparatively rare occurrence.

We have listed as "failures" all patients receiving any other anesthetic whatever; a total of 63, or 4.2 per cent (Table II). These include true failures, where injection was unsuccessful or the anesthesia insufficient, and also deliberate supplementary anesthetics. Some patients had a few whiffs of ether for discomfort rather than for actual pain, and a number of others were given

TABLE II

	SPINALS	FAILURES	PER CENT
1935-1939	71	7	0.9
1940	53	3	5.0
1941	71	2	2.7
1942	204	11	5.4
1943	401	18	4.5
1944	747	22	3.9
Total	1,547	63	4.7

TABLE III. FAILURES

Supplementary anesthesia	49
Version	5
Twins	1
Difficult forceps	4
Retained placenta	2
Premature giving of spinal	1
Repair rectovaginal fistula	1
Total	63

spinal with the intention of adding a small supplement for some special procedure, as previously mentioned. Others, in rapidly progressing second stage labor, were given some ether while the spinal was being injected, permitting a painless delivery and repair. The hospital records were not sufficiently exact to differentiate all the patients into these different categories. In Table III all undifferentiated cases are listed as "Supplementary anesthesia," a total of 49, many of which probably had a small amount of ether for discomfort or to facilitate the injection. In five cases of version and in one of twins, spinal anesthesia was given with the intention of supplementing if necessary. In four cases of difficult forceps delivery and in two of retained placenta, additional anesthesia was required, probably due to the duration of the procedure. The one case shown of premature giving of spinal was delivered several hours later under general anesthesia. A repair of an old rectovaginal fistula required supplementary anesthesia for closure of the perineal skin surface.

Since the anesthetic effect usually persists for a considerably longer time than is required for actual delivery, it has become the practice of our staff to perform quite extensive perineorrhaphies where indicated, including closure of rectovaginal fistulas, immediately following delivery. Although parturition may have been accomplished without laceration, a pre-existing condition can be repaired, thus saving a later gynecologic procedure with its attendant anesthetic.

In our series there were five patients who were recorded as having some form of shock. In one, shock was definitely due to severe postpartum hemorrhage, while in a second, third-stage bleeding seemed to be sufficient to cause a tachycardia and mild shock fifty-five minutes after injection of the anesthetic. The third patient, who had a pulse of 140, vomited profusely shortly after delivery and had difficulty in breathing. The fourth case had a mild postpartum shock with pallor, and a pulse of 120 shortly after delivery. The fifth case had an immediate drop in blood pressure after 50 mg. of novocain, marked pallor, and imperceptible pulse, with a heart rate of 64. In each case, the recovery was prompt with appropriate measures, and the child was normal.

The commonly accepted picture of procaine hydrochloride shock is "pallor, decreasing pulse rate, perspiration, nausea, vomiting, cyanosis, and convulsions" (Tovell). In the five cases which we have listed as showing some form of shock, there is only one which fits in with this picture.

There is another patient we should mention who had spinal anesthesia for rupture of membranes during induction of labor. As she was subsequently delivered without anesthesia, she is not included in our series. This patient was admitted to the hospital following an eclamptic convulsion and was treated conservatively for several days. Following unsuccessful medical induction, the membranes were ruptured under spinal anesthesia. During this procedure the patient appeared to be sleeping, had good color and normal respiration, but the blood pressure had dropped from a systolic of 182 to 40. Following the administration of the usual stimulants, a fairly rapid recovery occurred. We feel this must be considered a novocain reaction.

There have been no maternal deaths, either immediate or during the puerperium, from any cause. This group of patients includes a large number of seriously ill women, i.e., toxemias, infections of various kinds, prolonged labors, and difficult deliveries. Thirty doctors, most of them general practitioners, have employed spinal anesthesia for vaginal delivery during the period under review. In any series of over 1,500 obstetric patients, irrespective of the type of anesthesia employed, it would be reasonable to expect maternal fatalities. From these facts we conclude that small doses of novocain for subarachnoid block for delivery has certainly not increased the risk to the mother.

TABLE IV. STILLBIRTHS AND NEONATAL DEATHS AFTER SPINAL ANESTHESIA

	DEATHS	PER CENT	HOSPITAL PER CENT
1940	2	3.3	5.7
1941	1	1.4	5.6
1942	10	4.8	5.0
1943	23	5.6	4.8
1944	24	3.2	4.7
Total	60	3.7	5.1

There have been 43 stillborn babies and 17 neonatal deaths, giving a combined fetal loss of 3.7 per cent (Table IV). For the ten-year period, the combined percentage in our hospital is 5.1. It will be noticed that during the past five years, when spinal anesthesia has been employed with increasing frequency, there has been a progressive drop in stillbirths and neonatal deaths from 5.7 per cent in 1940 to 4.7 per cent in 1944.

In analyzing the 43 stillbirths, it was found that in 29 no fetal heart could be heard before delivery. Of these, six had a complete separation of the placenta. Of the remainder, there were six monstrosities. In only eight patients was there a reasonable chance of obtaining a normal baby, when the anesthetic was given. Of the eight, two were breech presentations in primiparas; one an internal podalic version after a long labor; one an abnormally large baby, one a twenty-seven week premature; one had the cord twice around the neck and very tight; and two were midforceps deliveries (Table V).

TABLE V. STILLBIRTHS

No fetal heart before delivery	23
Abruptio placentae	6
Monstrosities	6
Deaths during delivery	8
Total	43

Of the seventeen neonatal deaths, eleven had a considerable degree of prematurity; three had congenital abnormalities incompatible with life; one had hemorrhagic diathesis; one died of bronchopneumonia; and one from cerebral hemorrhage (Table VI).

TABLE VI. NEONATAL DEATHS

Prematurity	11
Congenital abnormality	3
Hemorrhagic diathesis	1
Bronchopneumonia	1
Cerebral hemorrhage	1
Total	17

Careful review of the hospital records fails to show the anesthetic drug as a contributing factor in any of these fatalities. From these figures it would seem reasonable to conclude that a baby born under spinal anesthesia has a better chance of living than it has when other anesthetics are used.

In order to obtain as accurate a record as possible of difficulties and postpartum sequelae, a questionnaire was submitted to those doctors, now available, who had used spinal anesthesia at the Mount Hamilton Hospital, and to the senior nurses most closely associated with its use.

From the replies to this questionnaire and from our own experience, certain facts have been ascertained.

1. The commonest postpartum complaint is headache. This occurs with sufficient frequency to be definitely annoying to the patient. It usually starts on the second or third day and rarely lasts for more than two or three days, and is much relieved by massage and manipulation of the neck and upper spine. It was impossible to determine the exact percentage of those suffering from this distress, but it is much less frequent than is commonly supposed. We have had no cases of headache prolonged for several weeks as have been reported.

2. Perineal discomfort is noticed earlier with spinal patients than with those having been delivered under general anesthesia.

3. Complaints of backache or distress at the site of injection have been very few. There were no infections at this point and no infections of the meninges.

4. There have been no injuries to the spine or to the nervous system.

5. Although it is impossible from our hospital records to produce statistical proof, there is a definite conviction among doctors and nurses alike that third stage and postpartum bleeding is considerably decreased.

6. The consensus of opinion is also quite definite that fewer babies require resuscitation, and analgesic drugs can be used more safely.

7. Repairs of episiotomies, lacerations, and even extensive perineorrhaphies can be done with greater care because there is no feeling on the part of the obstetrician of prolonging a general anesthetic.

8. The nursing care necessary in the delivery room and during the first few hours of the puerperium is markedly decreased, due to the active cooperation of the conscious patient. This has been of particular value in these days of overworked personnel.

9. The attitude of the patient is interesting. A few have been somewhat apprehensive before they have received their first spinal anesthetic, but there has been an almost unanimous desire for the same method for subsequent deliveries. Even a stillbirth or a monstrosity does not seem to prejudice the patient against it. The enthusiasm of the patient who had previously been delivered under a general anesthetic is very noticeable. We do not insist on this type of anesthesia unless the patient has an upper respiratory infection, evidence of fetal embarrassment, or there is prematurity.

10. The contraindications to spinal anesthesia in general apply in obstetrics, but there are none specific to the parturient state.

Summary

A report of 1,547 obstetric patients delivered with spinal anesthesia has been presented. There have been no maternal deaths. The stillbirths and neonatal deaths have been definitely fewer than with general anesthesia. There have been no infections or serious sequelae. The local popularity, both with patients and physicians, has increased steadily.

Conclusions

1. Spinal anesthesia in small doses is a safe anesthetic for vaginal delivery.
2. Fetal loss is decreased. It is of special value in premature babies.
3. Analgesic drugs can be used with less danger.
4. Rapid pain relief is experienced in over 95 per cent of patients.
5. Obtaining an anesthetist is unnecessary.
6. Third-stage and postpartum bleeding is diminished.
7. Nursing care is simplified.
8. Patients' satisfaction and approval are almost unanimous.

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Discussion

DR. SCOTT.—Until recently I had the same prejudice against spinal anesthesia in a pregnant patient as mentioned. I believe that this prejudice arose from the teaching of the late Dr. DeLee, who believed that a pregnant patient was a particularly bad risk for spinal anesthesia.

I now doubt the validity of this opinion, and recently have been doing my cesarean sections under spinal anesthesia. Only a small dose of anesthetic is necessary; indeed, the ordinary low cesarean section requires less anesthetic than does an appendectomy. We have not used spinal anesthesia for any other type of delivery, but today's presentation indicated that it is perfectly safe to do so.

I would like to ask Dr. Weaver at just what stage in labor the anesthetic was begun. He stated that one small dose was efficacious for about one hour. It is frequently difficult to be certain that the first stage of labor is entirely completed, and if one thinks that the second stage has commenced when this is not true, subsequent spinal anesthesia may be necessary.

I would like to ask, also, what analgesia is used previous to the spinal anesthesia, because analgesia during the first stage of labor may play some part in fetal mortality.

With one point I must disagree. This is the repair of previous obstetric injuries at the time of delivery under spinal anesthesia. The repair of a relaxed peritoneum can be done, but I doubt its wisdom. The tissues are congested, edematous, and soft. This makes for difficulty in getting a proper anatomic repair without undue tension. Moreover, the majority of such patients also have some degree of cystocele, and the repair of this at the time of delivery seems to me to be an unwise procedure.

I note that there are 23 practitioners using spinal anesthesia for delivery at Mount Hamilton Hospital. I would imagine that five or six of these men were skilled obstetricians, but the rest were general practitioners. I would like to know how the general practitioners

have been taught so that they have the necessary skill to give the spinal anesthesia themselves. Were they taught in small groups or did they pick up the procedure by simple observation?

Dr. Weaver also suggested that spinal anesthesia has some advantages in cases of premature babies, but in the first part of his paper he pointed out that the expulsive efforts are abolished and low forceps are employed almost routinely. In the case of premature babies, I believe that spontaneous delivery, aided by episiotomy, is preferable to the use of forceps wherever possible.

Finally, I am interested in the fact that for some time in Hamilton there was a decided enthusiasm for caudal analgesia, and a large number of patients were delivered under that procedure. At what stage in this series did caudal analgesia play a prominent part, and when did it begin to wane, and why?

DR. GEORGE STREAN.—What was the percentage of operative deliveries in this group compared to those who did not have spinal anesthesia, and what was the comparative morbidity?

DR. WEAVER.—As to the question of selection of patients—with the three or four of us who have done the majority of these cases it has become almost routine. Contraindications are infections of the back and old injuries of the spinal column. These hold good, but we do not feel that there are special contraindications in pregnancy.

In reply to Dr. Scott, we use this only as a delivery anesthetic. It is not intended as a labor anesthesia. As for skill and judgment of the operator—when it comes to a group of men such as general practitioners, one must expect that there will be some unsatisfactory results. We expected to find some who were not obstetric experts, and we were surprised to find how few there proved to be. There can be no doubt, I think, that any anesthetic agent with the power of novocain must be used with much respect. We are not trying to sell the use of this thing. We are merely making a report of our findings and are surprised to find that it has not apparently been dangerous to the mothers, nor, in our experience, to the babies.

The question of the repairing of old injuries is a controversial point. Difficulties are not nearly so great, as far as the posterior vaginal wall is concerned, as one would imagine. The wounds seem to heal with remarkable facility. Whether the repair of a rectovaginal fistula immediately following delivery is wise is a matter of opinion. I have done no anterior repairs.

As to teaching, I emphasized earlier that no effort was made to promote the use of this method. We have tried not to encourage its use. With us in Hamilton there is a good deal of consulting in obstetrics. Most of these we are delivering by giving spinal anesthesia. For premature babies, we use episiotomy and low forceps. This is a great deal safer than pounding on the peritoneum. It is a question of judgment. We use forceps for the after-coming head in breech delivery.

We used caudal analgesia a good deal for 480 cases a year or two ago. There was one death at that time.

As to the percentage of morbidity, I cannot say.

DR. TEW.—If this is used only as a delivery anesthesia, and you find that you have to deliver with forceps, why use it?

DR. WEAVER (Closing).—A good many of us will continue to deliver the majority of our primiparas with elective low forceps and episiotomy.

Fiftieth Anniversary Celebration of the Chicago Lying-in Hospital

Transactions of the Meeting held Oct. 29, 1945

UNDERGRADUATE AND GRADUATE INSTRUCTION IN OBSTETRICS AND GYNECOLOGY*

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IT SEEMS fitting that the teaching of obstetrics and gynecology should be a topic of discussion at these exercises commemorating the half-century mark in the life of the Chicago Lying-in Hospital. This Institution will forever be identified with the early growth and development of obstetrics in this country. Its place and that of its founder, the late Dr. Joseph B. DeLee, are secure in the annals of our medical history. Through the medium of his textbook, his clinic, and his teaching and training of undergraduate and graduate medical students, DeLee exerted a profound influence on this branch of medicine. It is fortunate for our field in general and for this Institution in particular, that his successors, Drs. Fred L. Adair and William J. Dieckmann, maintained his standards and ideals.

Just a decade ago I made a plea that the faculties and deans of our medical schools accord obstetrics and gynecology more recognition in the curricula of these institutions. At that time I ascribed the appalling maternal mortality in the United States to inferior and insufficient teaching of the undergraduate, and inadequate hospital training of the graduate entering the practice of obstetrics. My views were fully substantiated by the findings and recommendations of the Committee on Prenatal and Maternal Care of the White House Conference on Child Health and Prevention. Looking back over the past ten years, it becomes apparent that the recommendations of the White House Conference Committee played an important role in the notable reduction in maternal mortality observed during this period. Their findings as well as those of many studies conducted by medical societies and groups throughout the country made the medical and lay public aware of conditions needing urgent correction and improvement.

To refresh our memories I again quote from the report of the White House Conference of 1934:

"Instruction in obstetrics to medical students is a desideratum of prime importance in the determination of maternal morbidity and mortality. The better the clinical training of students in the art of obstetrics, the better obstetrics they will practice and this, in turn, will be reflected in improved results. Didactic teaching of obstetrics, in the United States, is and has been fairly satisfactory, save that it has been overstressed in many schools for

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want of clinical material. The need is not for less theory but for more clinical instruction." The Conference further recommended: "Unification of the departments of obstetrics and gynecology in medical schools and in all hospitals affiliated with and controlled by the university."

In order to evaluate our present status in the teaching of obstetrics and gynecology I have recently written the deans of all the Class A medical schools in the United States and Canada and have studied the catalogues of each of these institutions. Of the deans to whom my inquiry was directed, 71 gave me full data and answers to all questions. The information thus gathered from 71 of the 75 Class A medical schools offering the full four-year course, forms the basis of this presentation.

Combined Departments of Obstetrics and Gynecology

The present survey shows that of the 71 medical schools which gave complete answers to my inquiries, 51, or 73.2 per cent, have combined departments of obstetrics and gynecology, leaving only 20 schools where the two branches of our specialty are separated from one another, and it is encouraging to note that of the latter group there are only three instances where gynecology is a subdepartment of surgery.

TABLE I. COMBINED OR SEPARATE DEPARTMENTS

SCHOOLS AND DEPARTMENTS	NUMBER OF SCHOOLS	PERCENTAGE OF TOTAL
Medical schools studied	71	
Combined department of obstetrics and gynecology	51	73.2
Obstetrics an independent department	20	26.8
Obstetrics a subdepartment	0	
Gynecology an independent department	17	28.2
Gynecology a subdepartment of surgery	3	4.2

It is significant that almost every year we have one or more applications to positions on the residency staff of the New York Lying-In Hospital from graduates who have had hospital training in a separate department of either obstetrics or gynecology and who realize, unfortunately late in their training, that they need adequate preparation in the whole field of obstetrics and gynecology as a specialty. It is to be noted, likewise, that our American Board of Obstetrics and Gynecology presumes requisite training in both branches. As I have previously done so, it is not my purpose at this time to discuss the arguments of the few remaining "isolationists" as to why obstetrics and gynecology should be separate. These arguments have been more than adequately answered by the White House Conference Committee as well as by others. Suffice it to say that "obstetrics and gynecology are so intimately related as to be inseparable." It is to be hoped that private interest, tradition, or lack of a broad vision will not continue for too long to keep these two separate in the few remaining schools where today such is the case.

Medical School Curricula

In the British Isles all clinical instruction in medical schools is divided into three equal parts—medicine, surgery, and obstetrics and gynecology. Mid

wifery and the diseases of women constitute one-third of all final and qualifying examinations and, as Berkeley pointed out, are probably the most important of the three divisions because they deal with the well-being of those supplying the nation with citizens. He states, "The Medical Act draws, and knows, no difference between medicine, surgery and midwifery." Likewise, in the Scandinavian and German universities, obstetrics and gynecology have a prominent place in the undergraduate teaching schedule.

TABLE II. AVERAGE HOURS OF INSTRUCTION

SUBJECT	NUMBER OF HOURS	PERCENTAGE OF TOTAL HOURS IN THESE SUBJECTS
Obstetrics	279	14.9
Gynecology	136	7.3
Obstetrics and gynecology	403	21.6
Medicine	863	46.1
Surgery	604	32.3
Total	1,870	100.0

In Table II one sees the hours of instruction in the three main clinical branches. It should be noted that in the case of six schools it was difficult to translate the time allocated to practical obstetrics and gynecology in terms of hours. In these schools the student is not required to reside in the hospital and devote full time for a given period to obstetrics and gynecology, but must observe and attend a given number of deliveries or operations. However, even allowing for such errors in the study where the time actually allocated to obstetrics and gynecology is undoubtedly more than shown in the table, it is clear that in the majority of our American and Canadian schools this subject does not receive sufficient recognition in the curriculum. This is particularly true in the case of practical clinical work in obstetrics and gynecology. The average hours for medicine, surgery, and obstetrics and gynecology are 863, 604, and 403, respectively. Obstetrics and gynecology occupies 21.6 per cent of the total time given to these three divisions of clinical instruction. The average ratio of obstetric to gynecologic hours of teaching is two to one.

It must be clear to all of you why I am concerned about the apportionment of time in our curricula to these three subjects. I am not unconscious of the fact that the period of instruction does not tell the whole story, as it does not inform one regarding the type, caliber, and efficiency of that instruction. On the other hand, it gives an index of the amount, and practical aspects, of that teaching. It stands to reason that the student receiving 600 hours of instruction and required to reside two months in a hospital in order to devote full time to obstetrics and gynecology has a far greater opportunity to acquire a fundamental

TABLE III. DISTRIBUTION OF HOURS OF INSTRUCTION

SUBJECT	AVERAGE NUMBER OF HOURS	LIMITS OF NUMBER OF HOURS
Obstetrics	279	152 to 730
Gynecology	136	28 to 337
Obstetrics and gynecology	403	200 to 882
Medicine	863	400 to 1,526
Surgery	604	242 to 1,103

knowledge of that subject than the one with one-third that number of hours of instruction, no hospital residence, and only an "observation" course in the practical aspects of the subject.

You will observe that the minimum hours of instruction in this branch of medicine is 200, while the maximum is 882. The distribution of the required hours in obstetrics and gynecology is shown in Fig. 1, from which it will be seen that the large number of schools (36 per cent) offer between three and four hundred hours during the clinical years of instruction.

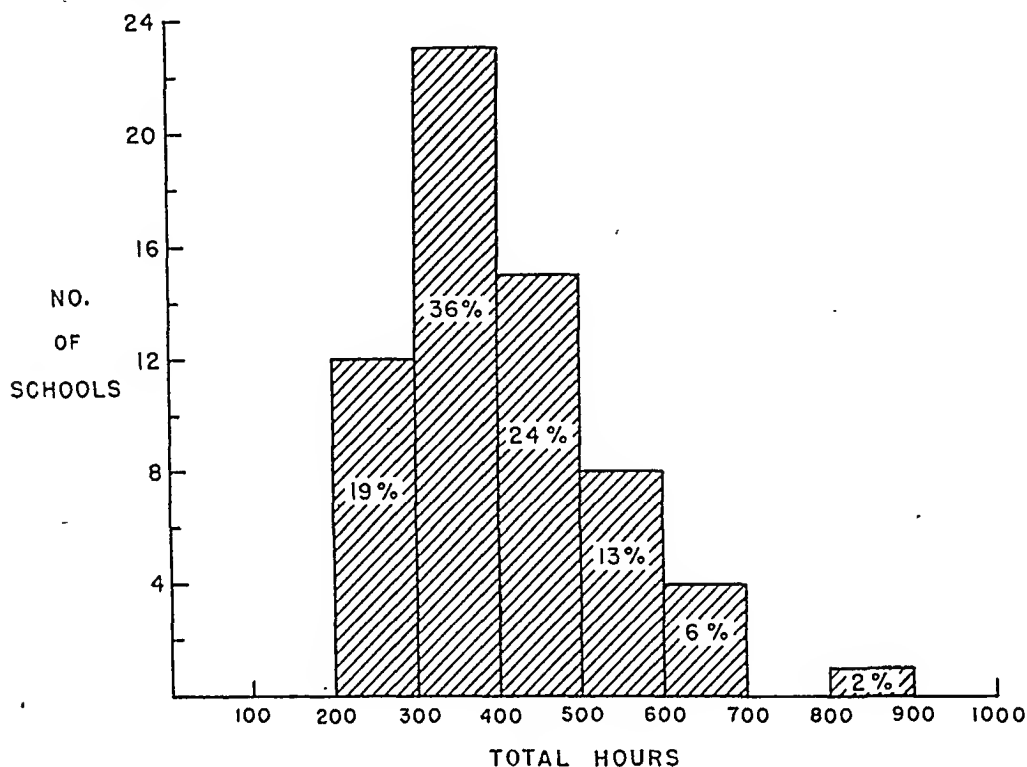


Fig. 1.—Hours required in obstetrics and gynecology (data from 63 schools).

In the next graph (Fig. 2) is recorded the number of hours required in our specialty, expressed as a percentage of the total hours of instruction in the three major clinical divisions, medicine, surgery, and obstetrics and gynecology. It is to be noted that only 6 per cent of the schools accord obstetrics and gynecology a place on a par with the other two branches, while the majority of schools allocate to obstetrics and gynecology from 20 to 25 per cent of the total hours.

Although there is this wide discrepancy as shown above, I was pleased to find that in 20 schools, obstetrics and gynecology was approximately on a par with surgery. This is a great improvement over my findings of ten years ago. At that time I wrote:

In considering the maternal and fetal mortality in the United States, I believe that the chief factor which is responsible for our appalling results is the inadequate teaching of obstetrics and gynecology in most of the medical schools of our country. . . . I am firmly convinced that better obstetrics can be realized only through two factors, firstly, by far

more thorough teaching of our specialty in the medical schools, and secondly, by better hospital training in obstetrics for the young graduate who will sooner or later be called upon to deliver a woman of her child. I believe that obstetrics and gynecology should be on a par with medicine and surgery in the curricula of our schools.

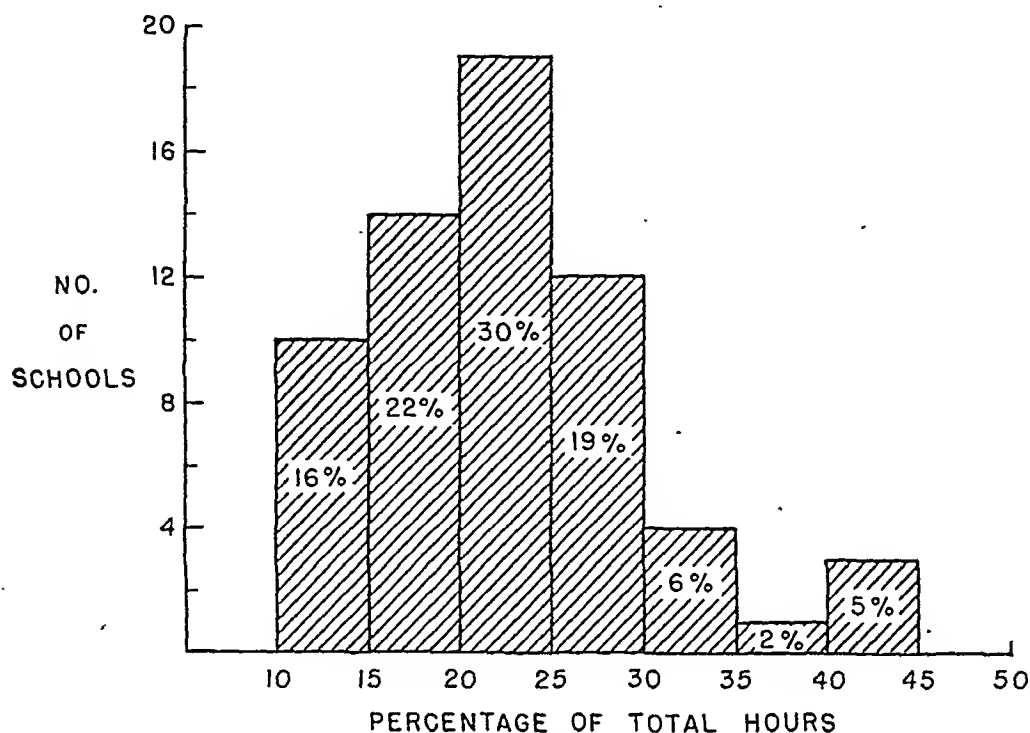


Fig. 2.—Hours required in obstetrics and gynecology as percentage of total hours required in medicine, surgery, and obstetrics and gynecology (data from 63 schools).

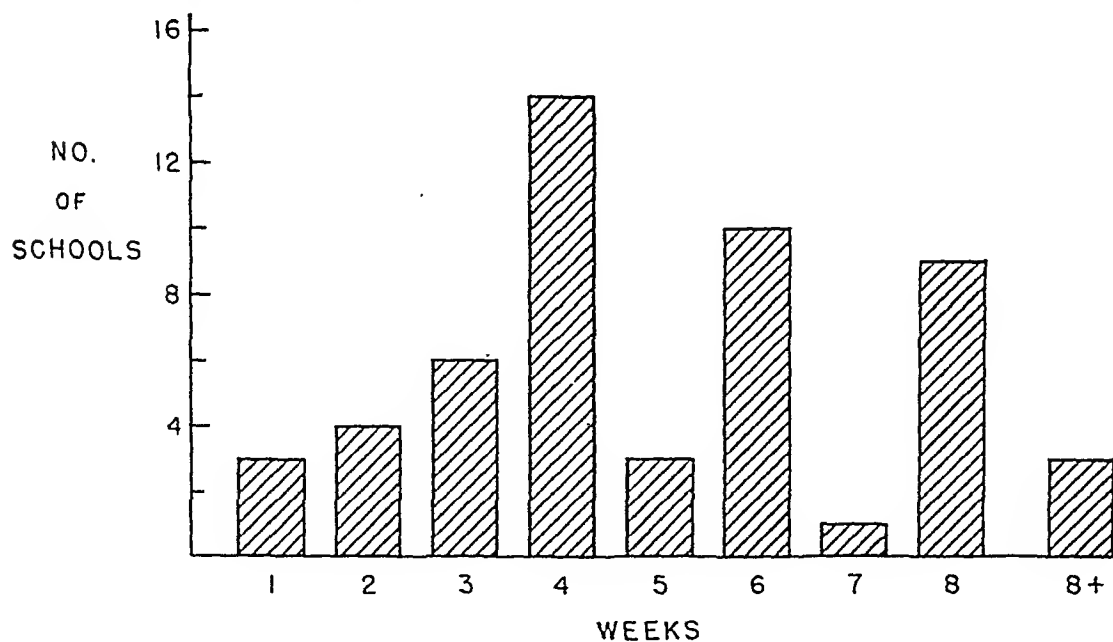


Fig. 3.—Weeks of residence required in hospital (data from 53 schools).

Today, at least 79 per cent of the 71 schools require that the student live in the teaching hospital, devoting full time to the practical work in obstetrics and gynecology, or in obstetrics. This residency period varies from one to eleven weeks, with an average for all schools of approximately five weeks. Were

TABLE IV. PRACTICAL OBSTETRICS AND GYNECOLOGY

PRACTICAL WORK.	NUMBER OF SCHOOLS	PERCENTAGE OF SCHOOLS
Required	56	78.9
Optional	4	5.6
No Data	11	15.5
Total	71	100.0

this average eight instead of five weeks, it would more nearly conform to the White House Conference recommendations and so meet the need for more clinical instruction in obstetrics and gynecology.

It is also most encouraging to observe that nearly all schools give a course in manikin and that 62 per cent of the medical colleges offer a special course in obstetric and gynecologic pathology; although, on the other hand, only 29.6 per cent of schools have a special course in obstetric bacteriology and infection. It is hoped that the next ten years will see a like improvement in this very fundamental clinical application of bacteriology and infection.

TABLE V. SPECIAL COURSES IN OBSTETRICS AND GYNECOLOGY

COURSE	NUMBER OF SCHOOLS	PERCENTAGE OF TOTAL SCHOOLS
Pathology	44	62.0
Bacteriology	21	29.6
Manikin	64	90.1

The study of the 71 schools reveals that in 30, or 42.3 per cent, obstetrics and gynecology is on a full-time or modified full-time system. In 40.6 per cent of the schools the three clinical divisions, medicine, surgery, and obstetrics and gynecology are on full-time or modified full-time, while in only 7.2 per cent are medicine and surgery, but not obstetrics and gynecology.

This usually indicates that the head and one or more of his assistants devote their full time to instruction, research, and care of patients within the department. My inquiry shows further that several schools contemplate the establishment of a full-time system. It should be explained that in this system, as originally proposed by Welsh and his associates and as established in most instances, part-time or attending doctors are utilized to the fullest in all three functions of the department, namely, care of patients, teaching, and research. This promotes and enables close integration and cooperation between the department and the practicing medical profession, thus materially strengthening the former, while enabling the latter to work in a university atmosphere with its many opportunities for development and improvement in knowledge and skill. It is indeed encouraging to note the increasing number of clinical departments in our universities embracing the full-time or modified full-time system.

Maternal and Fetal Mortality

A comparison of our national statistics for the year 1933 with those for 1943 reveal a reduction in maternal deaths of from 6.2 to 2.5 per 1,000 live

births; while the fetal mortality for these two years are 37.0 and 26.7 per 1,000 live births, respectively.

It is the usual custom to express maternal mortality as a ratio per thousand live births, for the reason that fetal deaths (including abortions, ectopic gestations, and stillbirths) are very incompletely reported. A table for 1940, appearing in the Report of the Subcommittee on Maternal, Stillbirth, and Infant Mortality of the Committee on Statistical Practice of the American Public Health Association, reveals the complete lack of uniform legislation and practice in the various states and cities in the reporting of stillbirths. Since 1939, the City of New York Department of Health, recognizing the inaccuracy of this general custom, expresses the maternal mortality from causes associated with pregnancy and childbirth as a ratio per 10,000 reported terminated pregnancies, a practice we have employed at the New York Lying-In Hospital for the past thirteen years. Should all vital statistics throughout the country be so recorded, we would have an accurate index of the loss of life in women undertaking pregnancy. The maternal and fetal mortalities are graphically shown in Fig. 4.

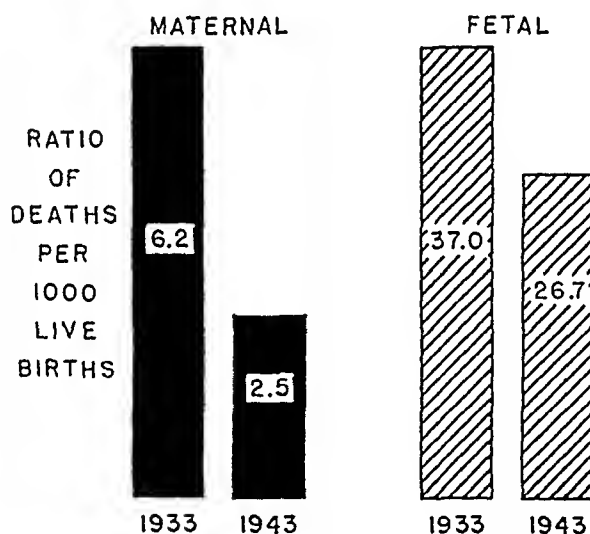


Fig. 4.—Mortality rates in the United States.

From these rates, it is clear that the maternal mortality has been markedly reduced, although there is still room for improvement, and this is particularly true in certain areas and sections of this country. Without question, the good results so far attained are in large measure due to the improvement observed in undergraduate and graduate teaching and training. The excellent efforts of city, county, state, and national medical societies and lay groups are further responsible for this reduction in maternal mortality.

On the other hand, it appears that equal attention and effort have not been focused on the offspring. A fetal mortality of 26.7 per cent is far too high and constitutes a loss of life so great that it becomes an outstanding challenge to modern medicine. When one considers that this death rate does not include abortions and ectopic gestations, it is evident that the actual loss of offspring is far greater than indicated by the figures. The Department of Health of the City of New York requires the reporting of any deadborn fetus, regardless of

the period of gestation, and on this basis the fetal mortality in New York City for the year 1944 was 81.5 per 1,000, a figure more accurately expressing the actual loss of fetal life than the commonly used "stillbirths per 1,000 live births."

Time does not permit a discussion of the preventable causes of fetal death; suffice it to say that I firmly believe that our medical schools and hospitals, through better and more adequate teaching and training of both undergraduate and graduate, will have to assume the responsibility for the improvement which must be brought about within the next decade or two.

Those of us, responsible for large gynecologic hospital services are only too well aware of the great number of patients, attending such services, who have had most inadequate previous medical attention. The reduction in preventable illness and death in this group is likewise dependent upon better preparation of the doctor and gynecologist of tomorrow. Anyone in the practice of gynecology becomes discouraged at times at the ever-present failure of early recognition and diagnosis of malignancy on the part of licensed doctors. Refresher and postgraduate courses, medical society meetings, and dispersion of information to the laity are factors designed to improve the situation and reduce or eliminate preventable deaths among women; but to accomplish the desired ends, we must add to these forces the more fundamental and far-reaching elements of sound and adequate undergraduate and graduate teaching, and training in gynecology.

The desired curriculum and training in obstetrics and gynecology will vary with each institution because of the inherent and physical characteristics incident to each medical school and hospital. However, it seems to me that we should all strive for a certain minimum. From the above reported study of our medical schools, it becomes clear that in about 20 per cent of schools the teaching and training of the undergraduate may be considered adequate, while this cannot be said about the other 80 per cent.

Undergraduate Instruction in Obstetrics and Gynecology

What should all schools strive for? In answer to this question may I express my opinion in the form of the following requirements:

1. Obstetrics and gynecology should be a combined department. If this is impossible or impracticable because of inherent or traditional characteristics of the institution or because of available hospital facilities, the two departments, independently administered, must be closely integrated in both teaching of medical students and training of graduates. In no instance, should either obstetrics or gynecology be maintained as a subdepartment of surgery or some other branch of medicine.

2. The time allocated to obstetrics and gynecology must be equivalent to that allowed for general surgery and general medicine.

3. A special course in obstetric and gynecologic pathology is an absolute essential. Similarly, bacteriology should have a place in the teaching schedule in a department of obstetrics and gynecology.

4. Each medical student must be required to reside in the hospital for a minimum period of from six to eight weeks, devoting his full time during that

period to practical obstetrics and gynecology. A requisite number of deliveries attended or performed is no index of the value of the practical work afforded the student. In the paper referred to above, I outlined in detail a course of instruction and practical experience embodying these requisites.

Graduate Instruction and Training in Obstetrics and Gynecology

I should like to stress once more that anyone desiring to enter our branch of medicine must be prepared to devote four to five or more years to hospital training in obstetrics and gynecology. The requirements of the American Board of Obstetrics and Gynecology are in line with this. Before the war the residency training in obstetrics and gynecology in our hospital was five years and we hope soon to be able to return to that schedule of training. This appears to me to be the minimum amount of time in which the average young graduate can acquire the knowledge and experience essential to practice our specialty. In this system of training the young intern spends his first year primarily in obstetrics, while the second year is devoted to gynecology and a small amount of obstetrics. During his third year he assumes duties of greater responsibility, such as having charge of the registrations and house staff of the outpatient or dispensary and of obstetric wards, and working on the gynecologic wards and operating rooms. His fourth year he is first assistant resident, spending six months in obstetrics, where he sees, supervises, and does a great deal of abnormal obstetrics, and six months on the gynecologic wards and operating rooms. He also spends a great deal of time in the subdepartment of gynecologic pathology, having had an introduction to this work during his third year of training. His fifth year he becomes the resident obstetrician and gynecologist.

In conclusion, I wish to appeal to the deans and faculties of our medical schools in which obstetrics and gynecology are still given a place distinctly secondary to either medicine or surgery. These schools must share part of the responsibility for our continued high fetal mortality throughout the country, a maternal mortality that must be lowered still further, and for the many deaths from the diseases of women resulting from gynecologic practice not consonant with early and correct diagnosis and adequate prophylactic and curative treatment. The family doctor usually does not practice surgery and most frequently has time to consult another physician or internist. On the other hand, he invariably delivers women and cares for the ills of women. Thus he assumes a great responsibility, the lives of both mother and child. He often and usually starts as a general practitioner without postgraduate hospital training in obstetrics and gynecology. It therefore becomes imperative that his undergraduate instruction and training in this field be as adequate as possible. It is for this reason among others previously pointed out, that I ask these deans and faculties to restudy their curricula and accord obstetrics and gynecology a place at least on a par with surgery, a branch of medicine which scarcely anyone today practices without previous postgraduate hospital training. Lastly, I also appeal to our hospitals in general, and to our university or university-affiliated hospitals in particular, to afford adequate house staff training, consisting of at least four and preferably five years in obstetrics and gynecology.

FUTURE PROSPECTS FOR OBSTETRIC CARE IN THE UNITED STATES*

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BEFORE starting on my remarks, I would like to express my appreciation to you for inviting me to take part in the celebration of the Fiftieth Anniversary of one of the great events in the history of obstetrics in this country. I want also to take this opportunity to congratulate the Chicago Lying-in Hospital and the University of Chicago on the many contributions made by the hospital and its staff to the science and art of obstetric care, and to the understanding of how maternity care of the highest type can be made available to every mother. When the Children's Bureau came into being in 1912, the Chicago Lying-in Hospital was already in its 'teens, and through its able leadership was assuming an important place in American medicine. In the early years of its existence, the Children's Bureau was able to look to this hospital and to Dr. DeLee for assistance and inspiration. I would like especially to take this occasion to pay my personal respects to your professor emeritus, Dr. Adair, and thank him in behalf of the Children's Bureau and the people of this country who have profited in untold ways through the counsel and advice and stimulation given to us in the Children's Bureau through the last two decades.

Recently, I have been told that plans are being made for the development of a course in advanced maternity nursing at the University of Chicago which will be directed toward the preparation of maternity nursing specialists. I am delighted to know that the personnel and facilities of this recognized center of medical education are to be made available for the graduate instruction of well-qualified nurses. We will continue to look to this hospital and medical school, and its medical and nursing staff, and to the Committee on Nursing Education for newer knowledge and inspiration in the science and art of obstetrics, and for leadership in the study and understanding of the problems of the economic and social application of that knowledge.

The subject that I have been assigned today is one which I have discussed on a number of occasions. Today I come before you under conditions that demand the most courageous planning in health fields in the history of the nation and of the world. The combat phases of the war are over. We are approaching a peacetime era charged with potentialities for good or evil such as we have never known before. Physicians and nurses and other technical workers, who have been serving with the military forces, are returning to civilian life, and are looking for new opportunities to serve the civilian population and to obtain additional training that will allow them to do this effectively and in accordance with modern scientific knowledge.

What we can do in the next decade to save life and better the health conditions of our people will be affected by many factors, economic as well as

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scientific. The citizens of this country are aware that great strides have been made recently in our knowledge of medical care, especially as the result of the concentrated war effort. They know that the health of our nation will depend in many ways on what is done for the health of the people of the world. But they also know that the health of the nation is primarily dependent on the protection of the health of each community, and on the facilities and care made available to each person living within that community. Our citizens, moreover, are not unaware of the fact that, if properly planned and organized, good medical care can be made available to everyone, no matter where they live, what their economic circumstances, what their race or creed or national origin. No group of people in the United States understands more clearly than do you who are assembled here today what it takes in terms of facilities and services to render good maternity care to the mothers of a community.

The war is over, and we are faced with the realization that the time is at hand to plan in concrete terms how we can go forward to assure to every mother in this country, as soon as is reasonably possible, that good maternity care about which you know so much.

Our knowledge of what to do to protect the lives of mothers during the maternity period and of their babies is very extensive, but it is not by any means complete. Research in the laboratory, clinic, and community is required. A better understanding of environmental factors, such as diet, can be obtained only through a combination of laboratory and community studies. The effect of physiologic and pathologic conditions in the mother on the development of the fetus and on the well-being of the infant must be further investigated. To these types of investigations should be added a whole series in the psychological and social fields. Today we are beginning to ask ourselves about the psychological effect of the separation of the infant from the mother during those first two critical weeks of the infant's life, and to weigh the medical and physiologic advantage to mother and infant of two weeks' care in a hospital against what appears to be the psychological disadvantage of this period of separation from the family. These and many other studies and investigations cry out to be done.

But of equal, and perhaps of even greater importance is the need to apply far more widely than we do today the knowledge and skills that we now have. That we have the skills to do an increasingly good job in saving lives of mothers and babies is made unmistakably clear when we study the excellent records of our best hospitals, and when we look at the mortality statistics in States where modern medical, nursing, and hospital care is available to a large proportion of mothers. One has only to realize that, if the maternal death rate in Minnesota in 1943 had been applicable to the whole country, nearly 3,000 mothers' lives would have been saved in that one year. If the infant mortality rate in Connecticut in 1943 had been applicable the country over, 31,000 infant lives would have been saved. Of these, approximately 19,000 would have been infants under one month of age. We have the knowledge and skill to save thousands of mothers from invalidism and ill-health that come as a result of inadequate obstetric care.

The saving of life is a bench mark we have used to measure progress year by year. This progress has been very great. Look back three decades at our national infant mortality rate of 100 deaths for every 1,000 infants born alive, and compare it with the most recent rate of forty. An even more dramatic drop in our national maternal death rate has occurred in the last decade, a decrease of 60 per cent. Today, Minnesota and Oregon can boast maternal mortality rates that are approximately one-third of the rate in the State, with the best record ten years ago.

Such progress is most gratifying. It means vastly better obstetric care today than a few years ago, and it undoubtedly means that large numbers of women are well today who would have been semi-invalids had the practices of some years ago still prevailed.

But we have no call to be smug about this. We are not doing all that we should do for either mother or baby. Of the 7,197 maternal deaths in 1943, 36 per cent were caused by infection, and 27 per cent by toxemia—a total of 4,529 deaths, or nearly two-thirds of the whole, from these largely preventable causes. Add to these the preventable deaths from hemorrhage, trauma, and shock, and we are confronted with the discomfoting fact that, provided the kind of care we know how to give had been given, more than 5,000 mothers' lives could have been saved in 1943.

Here is a job for the next decade. It will call for a well-organized state and nationwide maternity-care program, one that will include the best kind of obstetric service in health centers, hospitals, clinics, and in the offices of physicians practicing in groups or under a plan that will link them individually to the obstetric staff of a hospital or a clinic. Hospitals must be built in many areas to provide the additional 30,000 maternity beds that are needed to make possible hospital deliveries for all mothers. Most of these beds will be in general hospitals, but some rural areas may be best served by the construction of small maternity units connected organically with the larger general hospitals. Hundreds of new health centers will be needed where, among other types of service, prenatal and postpartum care can be given. In the more remote rural areas, and even in thickly populated cities, decentralized maternity clinics connected with a health center and a hospital will add to the convenience and safety of the mothers who live in such surroundings. Each of these physical units will have to be staffed with well-trained physicians, nurses, and medical-social workers. Each of the units should serve as a center for the education of the community in the essentials of good maternity care, for it is only as the people come to know through the efforts of physicians and nurses and other health educators what these essentials are, and how necessary they are to protect the lives and well-being of each mother and child that adequate care will be made universally available.

At the heart of the maternity-care program and of first concern to you and to me is the training of physicians and nurses in obstetric care. Nothing in our planning must be permitted to interfere with this. On the contrary, extension of the best kind of an obstetric training program must be the central theme of planning.

The brief three- to four-month training commonly given to young physicians in the usual rotating internships does not equip them to undertake the full range of obstetric practice. Three years of graduate training for physicians who are to be certified as obstetricians are now recommended by those who are qualified to judge, and nothing less should be regarded as adequate if the best obstetric care is to be made available to all women. To provide opportunities for such three-year periods of obstetric training will require the most careful planning by medical schools and hospitals. Clinical fellowships or salaried residencies with a level of compensation that is reasonable will have to be made possible if many more young physicians are to devote this amount of time to hospital training, and if sufficient recruits for training are to be found to meet the needs of an expanding maternity program. Upon such a plan as this will rest the orderly supply of obstetric interns and residents. Hospitals in the smaller cities that are not now provided with such resident staff would stand to gain immeasurably under an arrangement with a basic teaching or medical center if they are willing to collaborate in accepting clinical consultation and assistance from the staff of the obstetric department of the medical school. A two-way plan of teaching and service to patients could be inaugurated that would assure expert care of patients and continued incentive to physicians to increase their knowledge and skills.

Physicians in their practice of obstetrics in office, clinic, hospital, and community are assisted by nurses. Modern obstetrics could not be practiced without them. Adequate training in obstetrics is essential for all nurses. A good basic course should enable them to carry out the usual bedside or clinic duties. For the public-health nurse, such a basic course in obstetrics will usually be sufficient if appropriate supervisory service is available. Other nurses, however, must receive special preparation in advanced maternity nursing to equip them adequately to undertake certain broader responsibilities that will be increasingly required of them as obstetric practice improves. These responsibilities will include supervision of the obstetric care given by community public-health nurses and of the bedside and delivery room care rendered in hospitals; instruction in schools of nursing; and, in certain rural areas, full responsibility for the delivery of the patient under the general supervision of a physician. In the immediate future, the nurse who has had advanced maternity training will be in increasing demand as a maternity-nursing consultant in state-wide programs of maternity care, as a supervisor of a local maternity nursing service, as a supervisor in a hospital, and as a participant in demonstration and research projects related to obstetric care. The extent to which nurses with advanced training as specialists in maternity nursing will engage in the full practice of midwifery will depend on many factors, such as: the way in which obstetric medical practice develops, the rapidity with which hospital construction goes forward, and the need felt by physicians for such assistance in home or hospital. That nurses with such advanced training in maternity care and midwifery can fill an important place in obstetric practice in this country has been demonstrated. It is my conviction that there are many rural areas where this

type of joint practice by physician and nurse-midwife or maternity-nursing specialists is still needed and will be until our program of hospital care is fully developed in these areas.

A well-rounded program of maternity care offers great possibilities in saving the lives of mothers and in improving their well-being. Within a very few years we could again be boasting that our maternal death rate has been cut in half. However, even greater opportunity for future progress measured in terms of lives to be saved exists in the realm of the care provided for the newborn infant. In 1943, 70,000 (60 per cent) out of the 118,000 infant deaths were from prenatal and natal causes; 35,000 were the result of premature birth. Progress in saving life in the first month of life has been slow compared with that in the last eleven months of the first year. A large proportion of neonatal deaths is associated with the obstetric situation, and a considerable proportion occurs on the first day of life. The saving of these lives is a combined responsibility of the obstetrician and the pediatrician (or of the general practitioner who functions as both), and of the nurse trained in this special field. It is true that this is an area in which we need more knowledge and greater skills. Research into the causes of premature birth and how to prevent it is greatly needed. We are apt, however, to make this an excuse for not providing the care that we know how to give to newborn infants, and through which we could save many of these babies' lives. For example, we have the knowledge and skill by which we could save the lives of thousands of premature babies. But to save the life of a premature baby costs money; it calls for special equipment and for the expert, continuous, and devoted care of physician and nurse. It calls for intelligent preparation of the home and education of the mother by skilled nurses and social workers. It is an economic and social problem as well as a medical one. When all these resources are brought to bear, babies' lives can be saved. You know this well in Chicago.

One of the outstanding benefits of the emergency maternity and infant-care program for wives and infants of servicemen has been the provision of prolonged hospital care for many newborn, especially prematurely born infants. The cost of care of a premature infant is catastrophic when viewed in the light of an average family income. Unless a family happens to live in a city or town where hospitals have modern equipment and resources to care for premature infants free, as here in Chicago, the chances for survival of these infants are relatively slim. If premature babies are to be saved, if we are to continue to reduce our infant mortality rate as we have in the past, public provision for expert care of these babies will be necessary.

As is the case in so many other areas of medical care, it is not just a question of providing money to pay for care, important as that is. Facilities and services to give the care needed to save the lives of newborn babies simply do not exist in many places. It is, therefore, a question of making good care available throughout the country as well as paying for care. This means special training in the modern methods of care of newborn babies for the pediatricians and nurses who will assume major responsibility for this kind of care in hospitals and for teaching medical and nursing students. It means providing proper equipment

for the use of these experts in properly planned nurseries in properly constructed hospitals. It means increased knowledge of the subjects by all general practitioners and nurses. It means well-trained public-health nurses and medical-social workers to provide follow-up care in the home; it means good continuing medical care after the infant leaves the hospital.

Obviously, this cannot be done by just paying doctors' and hospital bills. It requires community and state-wide plans for the care of newborn infants, quite as much as it does for maternity care or for the care of older children; it means cooperation between medical centers and outlying hospitals in training physicians and nurses; it means a chain of services for pediatric and obstetric consultation, and advice extending from our largest medical centers to district and community hospitals and health centers, and thence finally to the smallest prenatal and child-health clinic in the most far flung of our rural areas.

In emphasizing the need for making medical, hospital, and health services available to all mothers and children wherever they live, I do not want to belittle the necessity of paying for these services adequately. If well-trained physicians, including specialists, are to be encouraged to practice in the smaller cities serving rural areas as well as in large cities, they must not only be provided with well-equipped hospitals in which they may work, but the remuneration that they receive for their service must be commensurate with the skills that they have and with the value of their service to the well-being of the community and the nation. The physician who saves the life of a mother or a premature baby in a rural hospital has rendered as great a service to the nation as does his similarly trained colleague in a large city in a similar case. Should he not receive equivalent remuneration? The same applies to nurses, laboratory workers, health officers, and others.

Hospitals to provide the type of care we all want must be paid on a cost basis. The service needed to provide good care (but not so-called "luxury" service) should be determined first, including, among other considerations, appropriate privacy for patients, and then the cost reckoned and spread among the whole. The quality of service provided to patients in hospitals supported from tax funds should be the best we know how to give. If these public hospitals were to be included in a program of maternity and child care that serves the whole public, the quality of care offered could be generally raised.

We know how to give good maternity care and good care to babies and children, but we have not devised the ways and means to make it accessible and available to all families. Hospitals and health centers have been lacking. Economic and geographic barriers stand in the way. Tradition, too, has established barriers that figure largely in discussions among the professions and among the people. On both sides some traditional practices, though certainly not all, must be replaced with new ones. For instance, if care of high quality is to be made available to all, individual practice must be replaced to a large extent by group practice whether in a hospital and clinic setting or in the setting of a privately organized group of physicians who are banded together to improve their service to their patients. Both of these methods of group practice are well known today, but do not exist everywhere. Few small cities have either type.

still fewer, both. Group practice must become the common method of providing care if care is to be as good as we know how to make it, and the groups must include not only general family doctors, but also the specialists needed by the average family at frequent intervals, such as the obstetrician and the pediatrician. Other specialists can be made available through larger groupings.

The family doctor in our smallest towns and villages must also belong to such a group, even though the specialists of the group, and the hospital and the diagnostic clinics, are located in a centrally situated town and the general practitioners are located on the periphery. Under such an arrangement the group practice must exist in fact, and not in name only, if the rural people are to be served adequately. There must be a two-way exchange of consultation and service between a rural or small town family physician and the central headquarters' staff of the hospital and clinic. The community, maternal, and child-health service, and the local health centers should be important connecting links in the chain that binds rural physicians to the central group.

To make such a plan of small city and rural group-practice work, hospitals and clinics, health centers, maternity units, and child-health clinics must be constructed and equipped in many areas. Plans for such construction, and the construction itself, could be undertaken if legislation now pending in the Congress were enacted.

To do all this, to create the plan, construct facilities, train personnel, and provide adequate remuneration for care will take money—money that must come from some pool into which all citizens contribute so that all families may be served. Some form of nationwide financing, through general tax funds, insurance funds, or both, will be necessary in order that the average family, no matter where they live, may be sure in advance that the burdens of the most of maternity care, and of care of the newborn baby and of the older child will not have to be borne as a lump sum charge on current resources when pregnancies occur or when sickness strikes. Since the saving of the lives of mothers and infants, and the normal growth and development of children have long been matters of national concern undertaken in the public interest, it seems right that a program of care designed for these purposes should be a charge on our general tax funds, shared in by all the people. It also seems right that any father and mother should be able to participate in the benefits of such a program for their children, if they wish to do so, without barriers of any sort just as they have the right to public education of their children.

Children are the most valuable and yet the most vulnerable group in our whole population. The recent war experience of Selective Service has re-emphasized how much we have yet to do if children are to reach maturity as sound in body and mind as is possible with present-day knowledge. Recent experience with the emergency maternity and infant-care program for wives and infants of servicemen has shown what concentrated effort can do in the way of making somewhat better care available for a selected group in the population. That the level of maternity care in many maternity homes and hospitals has been raised because minimum requirements for care under this program were

established on a nationwide basis is, I believe, unquestioned. It is also significant that, assured that their hospital care would be paid for, 90 per cent of the wives have had this type of care, as compared with 72 per cent of the total population in 1943. Obviously, physicians and patients both prefer it. Furthermore, great good has occurred because thousands of mothers have come to the attention of public-health nurses through this program who otherwise would not have had this help. None of these gains could have been made so rapidly without a planned program.

The emergency maternity and infant-care program, however, as a wartime measure has had certain serious organizational weaknesses that should not be carried over into a long-time plan, because sooner or later they would prevent improvement in quality of care. The most striking of these was the necessity to accept in many areas hospitals that met minimum requirements but not established standards and the services of general practitioners who, through no fault of their own, must practice without the advantage of hospitals, diagnostic clinics, or the aid of specialized obstetric or pediatric consultation. In some areas the shortage of maternity hospital beds and the lack of consultants could not be overcome for the emergency maternity and infant-care program in wartime. The very nature of this wartime program required that existing conditions of practice had to be accepted if the main purpose of the program was to be served. The inability of administrative agencies to organize during the war the type of maternity-care program that is necessary to assure the highest quality of care possible is understandable. Obviously, the situation stemmed back to the stage of development of our medical practice before the war started.

The emergency maternity and infant-care program will cease when Congress declares the war emergency at an end. To date, more than a million mothers and sick babies have had care under the emergency maternity and infant-care program—approximately 900,000 mothers have had maternity care, and over 100,000 sick babies medical and hospital care. But now following V-J day the number of applications for care each month has begun to fall off, and with the separation of large numbers of servicemen from the armed forces during the coming months we anticipate a steady decrease in applications. The Children's Bureau has made no effort to continue this program for families of the men in service beyond the period when it can serve its original purpose well.

When the program ceases, there will be those who will be glad to "call it a day." There will be others, however, and I am one, who will hope that something better than we had before the emergency began will sooner or later come out of it. No one, or few, want this particular type of maternity-care program for the future because it is not good enough. But our experience with the emergency maternity and infant-care program is full of lessons that should not be lost when we plan for what comes next. The mistakes that have been made should not be repeated, the gains should find expression in what is to come.

To serve the mothers and babies of this country well, our future maternity-care program must be founded on policies and practices that will be sound as to use of public funds, that will protect the interests of the recipient of care and

the interests of those who furnish care, and that will, above all, provide assurance that the care given and paid for from public funds will be of the highest possible quality.

The maternity-care program of the future will, I hope, be one in which the nation can justly take even more pride than it has in its emergency program during the war. If this is to be so, there will be no barriers raised to the care offered, each mother will be entitled to care as her right, just as her child is entitled to his education. This nation will recognize that upon the maternity program, as upon the program for the health of children, rests much that is needed to safeguard its future strength and growth. No mother will be barred because of her color, her creed, or her national origin. The maternity program will not be limited to the poor; there will be no connotation in the way the service is given that it is "charity." The care will be available on a state and community-wide basis to any mother who chooses to apply for it, but no one will be compelled to take it. The care will be so good that any mother will want to apply for it.

We have the skills to do this; collectively we have the means to pay for it. What we need is a plan of action and the "green light" to go ahead.

A BLOOD BANK FOR A LYING-IN HOSPITAL*

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Boston Lying-in Hospital)*

DURING the second World War, the impression, fostered largely through articles written by laymen and published in the lay press, has risen among nonmedical people that blood plasma is an effective substitute for whole blood, not only in the treatment of battle wounds, but also in the injuries and hemorrhages which occur in civilian life. Every physician knows that this is not true. In pure shock much of the fluid part of the blood escapes into the tissues, but the total number of red cells remaining in the circulation is undiminished. Prostration results because the circulatory system is partially emptied of the fluid it needs for its proper functioning. A pump that is not full of water will not work. For example, with extensive burns shock may be extreme, but there is little, if any, loss of blood. In such cases of pure shock, the need is for restoration of the fluid part of the blood; and plasma supplies this need. In obstetrics, on the other hand, since hemorrhage is frequent and shock is rare, whole blood is required to restore the lost corpuscles, and plasma is only of occasional and temporary benefit. A woman with a postpartum hemorrhage may, in extreme cases, lose in a few minutes almost half her total blood volume before the bleeding can be checked. It is unlikely that a soldier wounded in battle who lost the same amount of blood in so short a time would live to reach a first-aid post, and it is equally unlikely that, if he did, any amount of plasma would save him.

When transfusions are needed in obstetrics there should always be on hand an adequate supply of blood donations—because four or five transfusions are often necessary. Before the war and the establishment of a blood bank, the Boston Lying-in Hospital depended on students of Harvard Medical School for its supply of donors. With the onset of hostilities, however, both the Army and Navy, in complete disregard of civilian needs, forbade all students under their command to act as professional donors. Since the great majority of medical students were in either of the Armed Services, the supply of such donors for all the hospitals connected with Harvard Medical School was immediately cut off. At the Boston Lying-In Hospital it became necessary to organize at once a proper blood bank, using as donors the relatives or friends of women who had either registered for confinement in the public wards or who had placed themselves under the care of the staff physicians as private patients. The hospital is indebted to Dr. Louis K. Diamond, hematologist, and to Dr. Arthur T. Hertig, pathologist and obstetrician, for the organization and maintenance of this blood bank.

From every registered ward patient and every private patient, a sample of blood is withdrawn at the time of her first visit. Part of this sample is used

*Read at the Fiftieth Anniversary of the Chicago Lying-in Hospital, October 29, 1945.

for a Hinton test for syphilis, and the remainder is sent to the Blood Grouping Laboratory where the group and Rh factor¹ are determined. The Blood Grouping Laboratory was established by three hospitals, of which the Boston Lying-in Hospital is one, and serves also those members of the medical community of Boston and New England who wish to take advantage of its facilities. The results of these examinations are entered on each patient's record and she is issued a card, which she is urged always to carry with her, stating her blood group and her Rh factor (Fig. 1). If the patient lacks the Rh factor, or, in

IDENTIFICATION CARD	
BLOOD GROUPING LABORATORY	
BOSTON, MASS.	
300 LONGWOOD AVENUE	TEL. ASPINWALL 5773 5930
<u>Mrs. Charles (Mary) Rowe</u>	
<u>17 North Street Boston, Mass.</u>	
IS BLOOD GROUP	<u>O(IV)</u> RH <u>POSITIVE</u>
SPONSORED BY	
BOSTON LYING-IN HOSPITAL	MASS. MEMORIAL HOSPITALS
THE CHILDREN'S HOSPITAL	MASS. GENERAL HOSPITAL

BLOOD GROUPING LABORATORY	
BOSTON, MASS.	
300 LONGWOOD AVENUE	ASPINWALL 5773 5930
<u>Mrs. John (Jane) Doe</u>	
<u>21 West Street Boston, Mass.</u>	
IS BLOOD GROUP	<u>A(II)</u> RH. <u>NEGATIVE</u>
IN CASE OF NEED FOR TRANSFUSION USE	
ONLY COMPATIBLE RH. NEGATIVE BLOOD	
SPONSORED BY	
BOSTON LYING-IN HOSPITAL	MASS. MEMORIAL HOSPITALS
THE CHILDREN'S HOSPITAL	MASS. GENERAL HOSPITAL

Fig. 1.

other words, if she is Rh negative, this finding is at once reported to the blood bank at the Boston Lying-in Hospital. The blood bank sends her a letter informing her that if she were to need transfusion it would be vital to her safety that she receive the proper blood. The letter also requests that she ask four donors—preferably blood relatives, since they would more likely be also Rh negative—to contribute a pint of blood apiece. Donors secured in this way are grouped and Rh tested at the blood bank. All Group O donors so obtained, whether Rh negative or Rh positive, are bled 500 c.c.; donors belonging to other Groups, whether A, B, or AB, are not used. During the year from Oct. 1, 1944, to Oct. 1, 1945, there were 385 donations, all Group O. Of these, 68.8 per cent were Rh positive, and 31.2 per cent were Rh negative. (Table I.) Should a patient whose relatives or friends have made donations to the blood bank require one or more transfusions, she receives blood free of charge up to the number of contributions existing to her credit. She pays, however, \$5 for processing each donation she receives, and a \$5 service charge for the use of the operating room and instruments. If she is transfused and has provided no donors, she is charged in addition \$25 for each 500 c.c. of blood she receives. It

TABLE 1. DISTRIBUTION OF RH POSITIVE AND RH NEGATIVE DONATIONS TO BLOOD BANK
OCT. 1, 1944 TO OCT. 1, 1945

	NUMBER	PER CENT
Total donations	385	100.0
Rh positive	264	68.8
Rh negative	121	31.2

will be seen, therefore, that the relatives and friends of Rh negative patients provide most of the donors for the blood bank. Rh positive patients, however, are encouraged to secure donations if they desire. Any patient who receives blood and who has not supplied donors may cancel this indebtedness later by doing so.

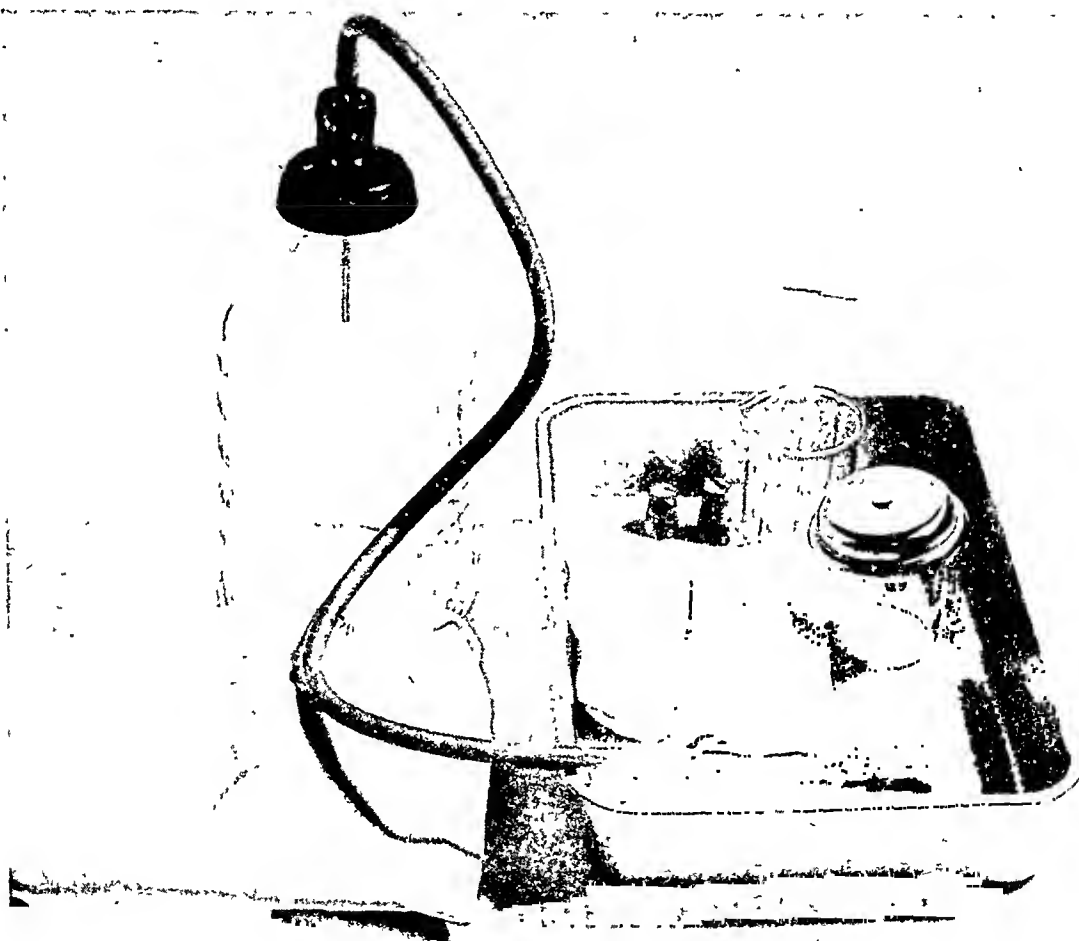


Fig. 2.

Blood donations are drawn by the blood bank technician or by a house officer, using the Fenwal closed system. The sterile bleeding set used for this purpose is kept always ready, and is shown with its envelope in Fig. 2. The Fenwal flask contains the so-called ACD mixture, consisting of sodium citrate, 1.48 grams; citric acid, 0.58 grams; and dextrose and hydrous, 1.72 grams, in a sterile aqueous solution of 75 c.c. The blood is drawn into and mixed with this solution to a total volume of 500 c.c. Two pilot tubes are prepared and labeled. One is attached to the flask; the other is sent to the Blood Grouping Laboratory

for checking with the blood bank findings. The Blood Grouping Laboratory uses the cells obtained from the clot for the Rh determination, and sends the serum to the State Laboratory at Harvard Medical School where the Hinton test for syphilis is performed. In case of emergency, the rapid Hinton test is used by the blood bank.

Before the blood bank was established there were three sources of delay in performing transfusions. The first was the difficulty in procuring donors immediately, the second was the time spent in grouping and Rh testing recipients and donors, and the third was the interval consumed in cross-matching. When the life of a patient might depend upon the prompt administration of blood, all these elements not only added to the risk, but also created an anxiety in the staff that on occasions seemed almost unbearable. Now, however, there is no delay. We already know the blood group and Rh factor of every patient who enters the hospital unless she represents an unregistered emergency case, and in such an event a few minutes' work in our laboratory suffices to obtain this information. We always have a supply of Group O, Rh positive and negative blood in the blood bank, which is on the delivery floor and only a few steps away. We do not need to cross-match the blood from the bank with that of the recipient because we have already inactivated the alpha and beta agglutinins in the O bank blood by suitable processing.

At the risk of repeating well-known facts, it is necessary to recall the characteristics of group O blood to explain how inactivation is achieved. The corpuscles of this type contain no agglutinogens, but in its serum are both the alpha agglutinin which combines with the agglutininogen in the corpuscles of A blood to produce agglutination, and the beta agglutinin which combines with the agglutininogen in B blood to produce the same effect, as is also the case with both agglutinogens in AB blood. In transfusion, serious or fatal reactions are almost always caused by agglutination of the donor's corpuscles. It is evident that this does not occur in Group O blood because its corpuscles contain neither of the agglutinogens. Its serum, however, possesses both the alpha and beta agglutinin, so that transfusion of O blood into an A, B, or AB donor may react with the agglutinogens of a recipient belonging to any of these three groups. Because of the discrepancy in volume between the transfused and recipient blood this seldom causes a reaction, but on some occasions it may do so; thus cross-matching is always advisable under such circumstances unless processed blood is used. If, however, the alpha and beta agglutinins in Group O donations can be inactivated prior to transfusion, blood so treated can be given to any patient regardless of his or her blood group. This is accomplished as soon as the blood is drawn by the addition to the flask under sterile precautions of 10 c.c. of Witelsky's specific A and B substances, which combine with the alpha and beta agglutinins in O serum to render them inert and thus capable of introduction into the circulation of A, B, and AB recipients without fear of serious reactions.^{2, 3} In the 228 transfusions to adults there were six reactions, a frequency of 2.6 per cent. There were no reactions among the 30 transfusions to infants. Only one of the six adult reactions suggested possible incompatibility. It was characterized by dyspnea and flank pain, and was stopped at 70 c.c.

without further untoward effect. The other five consisted only of chills and were probably due to improper cleansing of tubing, glassware, or needles. At present all such equipment is thoroughly washed before sterilization with distilled water from the blood bank still which is constantly tested for pyrogens by an electrical conductivity test.

Too much emphasis cannot be placed upon the absolute necessity of determining the Rh factor in all pregnant women, and in all donors who contribute blood to them. The serious and even fatal effects of repeated transfusions of Rh positive blood to Rh negative women are too well known to dwell on here, as are the same results when Rh positive blood is given even on one occasion to a Rh negative woman who has developed anti-Rh agglutinins by harboring in her uterus an erythroblastotic fetus. Moreover, we have seen several instances of women who have developed a high anti-Rh titer because of previous Rh positive transfusions before pregnancy given by general surgeons, and who have, as a consequence, produced thereafter nothing but erythroblastotic infants.

Processed blood is immediately placed for storage in the special blood bank refrigerator with revolving racks for Rh negative and positive blood. It may, however, be used immediately if necessary. Each flask is labeled with the name of the examining physician or technician, the donor's name, the serology, the blood group, and the Rh factor; in addition a transfusion sheet bearing the same data is filled out and filed, and if the blood is used this sheet is added to the patient's record. Blood in the refrigerator is held at 4° C. for not over twenty-five days. Up to the twentieth day such bank blood is said to be 85 per cent as effective as if it were freshly drawn, but its effectiveness falls during the next five days to only 70 per cent. Unless the blood is used before the twenty-fifth day it is discarded or used for pooled plasma, but since, for the reason already given, shock without hemorrhage is rare in our institution, our chief use for plasma is to supply the lack of blood proteins which occurs in pre-eclampsia.

Since the blood bank of the Boston Lying-in Hospital is adjacent to the delivery room, a transfusion may be started in a few minutes. While blood is being obtained from the bank, a needle is inserted into a vein on the anterior surface of the recipient's elbow, and a small amount of salt solution is allowed to run in until the blood is at hand. If difficulty is encountered in entering a vein and speed is imperative, blood may be administered at once into the bone marrow of the sternum or into the femoral vein by venipuncture. If one prefers to dissect out a vein, the internal saphenous is readily found just before it enters the femoral canal and is always of sufficient size, even in a collapsed patient, to admit a canula. When a large amount of blood must be given rapidly, we have on occasions used both arm veins and also the sternum.

Infants with erythroblastosis fetalis, although their blood is Rh positive, should be transfused with Rh negative blood because their blood may contain anti-Rh agglutinins. Even though their mothers' blood is Rh negative, it should not be used because it also contains anti-Rh agglutinins. Group O, Rh negative blood from donors who have not had erythroblastotic infants or who have never

been the recipients of Rh positive transfusions is used for this purpose. The most recently drawn blood in the bank is so employed. Seventy-five to one hundred c.c. are drawn off under aseptic precautions in the bacteriologic hood. The flask may be aspirated successively until its contents (500 c.c.) are used.

Two hundred fifty-eight, or 67 per cent, of 385 donations were used as transfusions during the year between Oct. 1, 1944, and Oct. 1, 1945; and, of this number, 228, or 88.4 per cent, were given to adults, and 30, or 11.6 per cent, to infants (Table II). Of the total transfusions, 68.2 per cent were Rh positive blood, and 31.8 per cent were Rh negative, thus following closely the Rh distribution of the donations. Seventy-five and four-tenths per cent of the adult transfusions were Rh positive, and 24.6 per cent were Rh negative (Table III).

TABLE II. TRANSFUSIONS

	NUMBER	PER CENT
Total donations	385	100.0
Total transfusions	258	67.0
Transfusions to adults	228	88.4
Transfusions to infants	30	11.6

TABLE III. DISTRIBUTION OF RH POSITIVE AND RH NEGATIVE TRANSFUSIONS

	NUMBER	PER CENT
Total transfusions	258	100.0
Rh positive	176	68.2
Rh negative	82	31.8
Transfusions to adults	228	100.0
Rh positive	172	75.4
Rh negative	56	24.6
Transfusions to infants	30	100.0
Rh positive	4	18.3
Rh negative	26	86.7

TABLE IV. BLOOD DONATIONS NOT USED FOR TRANSFUSIONS

	NUMBER	PER CENT
Total donations	385	100.0
Discarded	107	27.8
Used for pooled plasma	20	5.2
Total not used	127	33.0
Total Rh positive donations	264	100.0
Discarded	75	28.4
Used for pooled plasma	13	4.9
Total not used	88	33.3
Total Rh negative donations	121	100.0
Discarded	32	26.4
Used for pooled plasma	7	5.8
Total	39	32.2

Table IV shows that one-third of the donated blood was not used for transfusions. This represents a wastage which is common to all blood banks and which cannot be avoided, for if the bank is properly maintained, the supply should always exceed the demand. The advantages, however, in having in a lying-in hospital

not only at hand and readily available, an adequate supply of blood which may be safely and promptly administered far outweighs any such disadvantage. Moreover, since 500 c.c. is only about one-tenth of the average amount contained in the body of a normal, healthy adult, the loss to the individual donor is not great.

All blood used for transfusions at the Boston Lying-in Hospital is not from the blood bank. If no emergency exists, we prefer to use a relative, a friend, or a professional, especially if he is of the same blood group, for fresh unprocessed blood has a distinct therapeutic advantage. Most cases, however, are those of sudden and severe hemorrhage, and for them the ability to give blood at once without the delay of procuring donors, typing, and cross-matching has already proved a lifesaving measure.

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SOME CONTRIBUTIONS OF ENDOCRINOLOGY TO OBSTETRICS AND GYNECOLOGY*

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THE title of this address would be phrased more appropriately, perhaps, if it read, "Some Contributions by Obstetricians and Gynecologists to Endocrinology." Some of the most outstanding of these contributions have come from the University of Chicago and, in particular, from its Department of Obstetrics and Gynecology.

Endocrinology has been accepted as a faithful handmaiden of our specialty. We have learned that the varied genesiologic functions of woman are monitored by her endocrine system, and our expanding knowledge of the mechanisms of this system has given a foundation for the present "physiologic phase" of obstetrics and gynecology. Application of this new knowledge of gynecic physiology has clarified the etiology of many enigmatic disturbances of woman's reproductive processes, and has permitted correlation of them to functional aberrations of her endocrine system rather than to speculative diseases or to obstinate perversity. The conservative treatment of these functional vagaries with appropriate endocrine substances has rendered less frequent any recourse to function-destroying surgery and roentgenotherapy and, thereby, has preserved, and has effected, physiologic salvage of the childbearing function of countless women.

Historical Background

It is fitting on this occasion that we should pause to examine briefly the status of endocrinology and the concepts of gynecic physiology fifty years ago, when the Chicago Lying-In Hospital was founded.

*Endocrinology about 1895.*¹—Clinical endocrinology was a newborn itself when the first baby was born at Chicago Lying-in Hospital. Brown-Séquard, the Father of Clinical Endocrinology, had died the year before, in 1894. The *Journal Lancet* of April 7, 1894, in an obituarial editorial, had observed that "it is to the recently deceased savant that the medical world owed the initiation of treatment of disease by injection of animal extracts."

Brown-Séquard had described, in 1889, the rejuvenating effects which he had produced in himself—then 72 years old—by injections of an extract composed of blood of the testicular veins, of semen, of liquid from crushed testes, and of distilled water. Successful treatments of myxedema by injections of thyroid extract and by the oral administration of thyroid gland were reported respectively in 1891 and 1892. One year later, in 1893, a patient with "menopausal psychosis" was said to have been cured by the subcutaneous administration of ovarian juice. Organotherapy was well on its way!

*Address delivered at the celebration of the Fiftieth Anniversary of the Chicago Lying-In Hospital, University of Chicago, Chicago, Ill., October 29, 1945.

Knowledge, however, of the physiology, and even of the detailed anatomy, of no gland was complete in 1895.

An organic combination of iodine was recognized in 1895 as a constituent of the normal thyroid gland: here was the beginning of the fruitful studies of iodochemistry which still continue.

The adrenal medulla in 1894 was shown to contain a pressor substance and, two years later, this principle was isolated.

Although Brown-Séquard, in 1856, had concluded from experimental adrenalectomy that the adrenals were essential for life, no cortical extracts with life-preserving properties were prepared until 1927.

In 1893, experimental studies gave proof that the pancreas had an endocrine function and, three years later, the islet cells were shown to contain secretory granules.

The first complete anatomic and embryologic description of both pairs of the parathyroids was given in 1895 and, the following year, tetany was related to parathyroid deprivation.

In 1898, it was demonstrated that ovarian grafts, in previously oophorectomized women, reestablished menstruation, sexual desire, and a sense of well-being. Two years later, ovarian control of the female reproductive system was established; however, the same year of 1900 the members of the American Gynecologic Society heard the statement that "there is not one iota of proof that the ovary has any other function than to manufacture eggs."²

Although Kundrat and Englemann, in 1873, described cyclic alterations of the endometrium, these observations went unnoticed or were forgotten until Hitschmann and Adler, in 1908, rediscovered and amplified them. Accordingly, in 1907, in Kelly's and Noble's *Gynecology and Abdominal Surgery*, we find an illustration of a normal full-blown progestational endometrium labelled as glandular hypertrophy of the endometrium, and this condition (or as it was also called, glandular endometritis) was described as pathologic.

In 1893, it was shown that injury of the anterior pituitary increased the output of urine. The next year, acromegaly was correlated with hypertrophy and overactivity of the pituitary and a pressor action of pituitary extracts was demonstrated.

*Views on Menstruation and Ovulation About 1895.*¹—Now let us examine briefly some of the views on menstruation and ovulation which were current about 1895. The ovum-producing function of the ovaries was generally accepted. Most physicians believed that, in some way, menstruation was related to ovarian function. There were some dissenting views. Robinson,³ for instance, maintained in 1891 that menstruation was governed by so-called "automatic menstrual ganglia" which were situated in the walls of the Fallopian tubes and uterus, and that ovulation was quite unrelated to menstruation, menstruation occurring only when periodic and rhythmic peristalsis of the tubes was established.

Playfair in his *Science and Practice of Midwifery* (Sixth American Edition, 1893) observed: "That there is an intimate connection between ovulation

and menstruation is admitted by most physiologists, and it is held by many that the determining cause is the periodic maturation of the Graafian follicles."

Skene in his *Diseases of Women* (Third Edition, 1897) observed: "The function of the ovaries is primary in the process of reproduction. Their physiological activity precedes the uterine functions, and continues, as a rule, until the menopause, and possibly after it. Hence the functions of the other sexual organs appear to be responsive to the influence of the ovaries." Skene, however, in listing "certain conditions" which he held to be necessary to the fulfillment "of the laws of menstrual function" did not emphasize, in particular, the essentiality of the ovaries.

Although Heape, from 1894 to 1900, supplied factual data from his studies of the Macaque that ovulation and the presence of corpus luteum were not essential for periodic uterine bleeding—and these observations were confirmed by van Herwerden in 1906, who shot monkeys in their native jungles for study—the doctrine that menstruation was due to degeneration of the corpus luteum or failure of fertilization of the ovum ("primacy of the ovum") was destined to arise when Ludwig Fraenkel, in 1903, demonstrated that the corpus luteum had endocrine activity. Bischoff's studies⁴ (1842-1854), which incidentally had made it respectable for a single woman to have a corpus luteum by proving that its presence was not due to coitus or pregnancy, had supplied one authentic case record, however, which showed conclusively that periodic uterine bleeding was not relatable to the antecedence of a corpus luteum. As late as 1924, Novak⁵ observed, however, that "the weight of evidence . . . is overwhelmingly in favor of the corpus luteum as the ovarian factor responsible for menstruation."

Some Present Concepts and Clinical Applications

Any survey of the role which endocrinology plays in present obstetric and gynecologic thought and practice must be limited in its scope. A few of the outstanding concepts and clinical applications will be discussed.

Physiology of the Menstrual Cycle.—The isolation of estrogen from human ovarian follicles in 1925, by Edgar Allen and his associates, was the starting point of our present concepts of the menstrual cycle. (Progesterin, subsequently in 1936, was identified in human corpora lutea). Uterine bleeding, in 1926, was shown to follow a deprivation of estrogen, either resulting from castration after the middle of the cycle, or from the withdrawal of estrogen therapy, or its reduction to subthreshold amounts. It was shown also that this withdrawal bleeding could be prevented by estrogen therapy. Pharmacologic studies of estrogen and progesterin correlated the interval growth phase and the progestational differentiative phase of the endometrium as results of the respective actions of estrogen, and of estrogen and progesterin, during the menstrual cycle. Accordingly, a hormonal foundation was supplied for menstrual bleeding and for the endometrial alterations of the menstrual cycle.

Our present concepts of the mechanism of uterine bleeding rest fundamentally upon the cytologic and vascular studies⁶ initiated here at the University of Chicago by Professor Bartelmez and his group, which included O'Leary

and Markee. The detailed studies of Markee upon ocular endometrial implants in the monkey have afforded basic data upon the physiologic changes of the living endometrium.

The theory of menstruation, which, in my opinion, provides the best clinical tool for working with the diverse functional irregularities of uterine bleeding, is the one currently held by Markee.⁷ It is summarized. The cyclic waves of estrogen secretion by the ovaries cause characteristic growth of the endometrium. Regressional changes, which end in menstruation, occur when the blood estrogen levels fall to levels which are 50 per cent or less of those which characterize the peak of estrogen secretion. Progestin levels are not regarded as contributing significantly to endometrial growth or as being involved in the withdrawal phenomena which initiate uterine bleeding; however, the levels of progestin are adequate for endometrial differentiation and for other physiologic functions attributed to progestin. This "growth wave theory" of menstruation, accordingly, is applicable both to ovulatory and anovulatory cycles.

When estrogen levels become insufficient to maintain endometrial growth, regression begins. Regression may or may not end in bleeding, dependent upon the degree of estrogen deficit and upon the scope and rapidity of the regression.

When a critical fall in estrogen levels occurs, the following train of events ensues. Regression and decrease in the thickness of the endometrium produce characteristic changes in the spiral arterioles: increased coiling, knotting, and buckling. These result in stasis and anoxemia of the functional layer of the endometrium, which in turn cause necrobiosis, impairment of vascular integrity, and the liberation of a "menstrual toxin." This toxin produces vasoconstriction of the undamaged lower portions of the spiral arterioles. Bleeding occurs as the vasoconstriction effect on isolated arterioles wears out, and continues until the arterioles again become constricted. Menstruation ceases when a new growth wave of estrogen secretion begins and permits rec epithelialization by growth and reestablishment of an adequate circulation in the remains of the functional area.

Endometrial Biopsy and Anovulatory Bleeding.—The technique of endometrial biopsy has provided a simple, safe, and clinically practical method of gauging the quality of ovarian function.⁸ In 1931, Bartelmez observed that the total number of menstruating uteri studied histologically was so small that "no one can be justified in setting up a norm for the process."⁹ At present, however, many clinics perform routinely endometrial biopsy at the onset of bleeding when investigating functional disturbances of uterine bleeding and sterility. Accordingly, some clinics now have studied many thousands of endometrial biopsies, taken during bleeding.

Corner,¹⁰ in 1923 and 1927, submitted conclusive evidence that cyclic anovulatory bleeding occurred in the Macaque, and he listed several instances from the clinical literature which provided convincing evidence that a woman might bleed cyclically without antecedent ovulation. During the past decade, cyclic anovulatory bleeding has been diagnosed frequently by endometrial biopsies, and its causal relationship to some sterility and to many functional disturbances of uterine bleeding has been generally accepted.

The Time of Ovulation.—The preponderance of clinical data indicates that ovulation occurs approximately fourteen days before the onset of the next menstruation.¹¹ Endometrial biopsies taken immediately after the supposed time of ovulation commonly show early progesterational alterations.¹² Pregnanediol is not present in the urine until after the time of ovulation. Studies of basal rectal temperatures, when these are kept carefully throughout the menstrual cycle, permit a simple clinical method for timing ovulation.¹³ The characteristic rise in basal rectal temperature, which signalizes the postovulatory phase of the cycle, has been related to the action of progesterin. The data from records of basal rectal temperatures emphasize the fact that variabilities in cycle length concern the estrogen phase and not the progesterational phase, which appears to be consistently fourteen days in length.

Biology of the Vagina.—Studies of the biology of the vagina, prominent among which are those of Davis and Pearl,¹⁴ have related cornification of the vaginal mucosa, its glycogen content, and its acidity to the action of estrogen. These studies paved the way for an effective estrogen therapy of gonorrheal vaginitis of children, and of atrophic vaginitis of the aged, and supplied the rationale for estrogen therapy prior to and following plastic vaginal operations in postmenopausal women.

Cytologic studies of vaginal spreads have been used to gauge levels of ovarian function.¹⁵ Considerable histologic acumen is required for suitably stained preparations and their interpretation. A recent extension of this method has been its employment in searching for diverse, wandering cancer cells as an implement for the early diagnosis of genital cancer.¹⁶

Biology of the Cervix.—Glandular and stromal changes in the endocervix have been described during the menstrual cycle.¹⁷ These alterations have been related to the ovarian steroids. The suggestion has been made that these cyclic changes may be mistaken for low grade cervicitis. Estrogen liquefaction of the cervical mucous plug for reception of the spermatozoa, about the time of ovulation, has been established.¹⁸

Steroid Metabolism.—Urinary levels of pregnanediol, a metabolic product of progesterin, have been studied. These appear to be more reliable as an index of chorioplacental activity than of corpus luteum activity.¹⁹

Kenyon's fruitful studies²⁰ of steroid metabolism have emphasized the metabolic or extragenital effects of androgens, estrogens, and progesterin. The nitrogen, sodium, and water storage effects of these steroids play important roles in the physiology of pregnancy. Menstrual edema, doubtlessly, is related to sodium and water storage produced by estrogen and progesterin.

Studies of urinary 17-ketosteroids, which are end products of adrenocortical steroid metabolism in the female, have revealed significant reciprocities of ovarian and adrenal steroid metabolisms. The suggestion has been offered that the adrenal cortices serve as the "gonads of the aged," in view of the fact that there is an upswing in 17-ketosteroid excretion when ovarian function fails.²¹

Hormonal Pigmentation.—The hyperpigmentations of pregnancy, including that of the nipples and areolae, the linea nigra, chloasma, and the "mask of pregnancy," are due to the physiologic hyperestrogenism of gestation. The nongestational pigmentation of the areolae, nipples, and labia is also due to

estrogens. These facts are proved conclusively by the pigmentary changes which result from intensive estrogen therapy of young women with delayed sexual maturation. A recent study by Davis and his associates²² has emphasized that elements other than estrogen alone are involved in this pigmentary mechanism. These workers called attention to the fact that estrogens fail to produce pigmentation in women of menopausal age, and they made the suggestion that the functional status of the pituitary may condition the pigmentary response to estrogens.

Androgens and Virilizational Syndromes.—A large measure of our knowledge of androgens is due to the fundamental studies by Professor Koch, Professor Moore, and their associates. The physiologic import of woman's androgenic moiety, however, has not been established. It is likely that androgens in woman may have important extragenital roles. The consensus is that androgens play no significant part in woman's reproductive physiology; in other words, woman is a woman, not by virtue of her androgens, but despite them. An unfortunate tide of empiric androgen therapy in gynecology—now in its ebb—clearly established the relationship of androgens to the virilizational syndromes of woman. The irreversibility of clitoridal hypertrophy and the voice changes produced by androgen therapy, when the therapy was discontinued, parallel the course of these changes following successful surgical removal of an androgen-producing ovarian tumor. It is our opinion that, at present, none of the supposed indications for androgen therapy of woman warrants woman's exposure to possible virilization.

Functional Uterine Hemorrhage.—Functional uterine hemorrhage usually is associated with a disturbed ovaripituitary system, in which growth waves of estrogen secretion are altered, often with estrogen values teetering for long intervals at bleeding levels. Other manifestations of this changed function include a disturbance of the storage and release of luteinizing gonadotropin of the pituitary, a failure of ovulation, an absence of progestin from the hormonal mechanism of the cycle and characteristic alterations in estrogen metabolism.²³ The control of depleting hemorrhages in the young woman, in whom the preservation of childbearing function demands conservative therapy, has been, in the past, one of the most difficult and vexing problems of gynecology. The hemostatic action provided by oral estrogen therapy affords a prompt, inexpensive and conservative method of stopping a functional hemorrhage. Several series of oral cyclic estrogen and progestin therapy, given in a fashion similar to normal ovarian secretion, usually regulate the bleeding cycle and restore normal steroid metabolism and ovaripituitary reciprocities.¹ In my opinion, this therapeutic endocrine application has been the most fruitful of all those made in gynecology.

Incomplete Sexual Maturation With Absence of Bleeding.—This condition is due usually to an intrinsic incapability of the ovaries to be aroused to full adolescent function by the individual's own pituitary gonadotropins. As a rule, incompletely developed fetal ovaries persist in the adult epoch. The gonadotropic function of the pituitary is normal or commonly elevated. Oral estrogen therapy usually provides dramatic sexual, somatic, and cosmetic responses. The ovaries of these individuals, however, uniformly remain un-

responsive to gonadotropic therapy. Salvage of reproductive function is impossible.

Intercurrent Estrogenic Failure of the Ovaries.—Most intercurrent amenorrhea, which is not related to constitutional disease or to metabolic disturbances, is due to an intrinsic estrogenic failure of the ovaries, that is, a premature menopause. Regardless of the flowings which may follow oral cyclic estrogen therapy, or the more expensive estrogen and progestin injections, the ovarian status remains the same. Gonadotropic therapy usually fails to restore normal ovulatory functions.

Ovarian Sterility.—The routine use of the endometrial biopsy technique in the study of sterility has established that 5 to 15 per cent of wives of childless couples have ovarian sterility, i.e., bleed from estrogenic endometria.¹ Approximately one-half of these women may be restored to a fertile ovarian status by gonadotropic therapy.²⁴

The ability of equine gonadotropin to stimulate the human ovary was proved conclusively by Davis and Koff.²⁵ For the treatment of sterility due to anovulatory ovarian failure, we have found the cyclic and sequential use of both equine and chorionic gonadotropins to be necessary: we have called this regime, one-two cyclic gonadotropic therapy.²⁴ Unfortunately, this therapy requires injections and, furthermore, it may not be given for prolonged periods since it may provoke sensitivity phenomena and antihormone responses. Accordingly, its use is best reserved for trials at conception.

Toxemia of Pregnancy.—George and Olive Smith²⁶ have described characteristic hormonal disturbances in eclamptogenic toxemia of pregnancy. These include an elevation of serum chorionic gonadotropin, a progressive progestin deficiency, a similar concomitant estrogen deficiency, and a changed steroid metabolism which is characterized by an increased destruction of estrogens. These workers have attributed etiologic significance to their findings. Employing large doses of estradiol benzoate, progesterone, and pregnanediol, the Smiths were able to stabilize the hormonal disturbance of eclamptogenic toxemia and to improve the clinical state of their patients. They did not consider, however, their therapeutic regime to be yet clinically practical.

Application of the Smiths' studies to the toxemia of pregnant diabetics was made by Priseilla White.²⁷ Intensive treatment of this condition with estrogen and progestin doubled the fetal survival rate and brought it essentially to that of normal or nontoxemic diabetic pregnancies.

The Climacteric.—The hormology of the climacteric has been defined as typical of a gradual, intrinsic ovarian failure. This failure provokes a striking hypergonadotropic response of the pituitary, which may be used as a measuring stick of other ovarian failures thought to be intrinsic in the ovaries. A period of cortical hyperfunction, as evidenced by increased urinary 17-ketosteroids, seems to occur concomitantly with the increased gonadotropic function of the pituitary.²¹ The suggestion has been offered that the luteinizing gonadotropin of the pituitary may be responsible, not only for the formation of progestin by the corpus luteum, but also for the cortical elaboration of androgens, progestin, and their related 17-ketosteroids.

As grateful as estrogen therapy may prove to be to the climacteric woman, its use often has been too frequent and too uncritical, and its dosage schedules often have been too large and too haphazardly given. A few comments, accordingly, appear justified. Few climacteric women require estrogens. Estrogen therapy fails to cure basic psychopathies which may simulate climacteric disturbances. Injunctive therapy is no longer necessary; its psychologic approach is unhealthy. Infrequent injections of large amounts of estrogens are an ideal formula for keeping the endocrine system in a state of flux and chaos. When estrogens are employed, the usual daily dosage, in my opinion, should be no greater than the equivalent of one-half milligram of diethylstilbestrol. Therapy should be given cyclically, with a week of no therapy intervening between series of treatment. These precautions will prevent upsetting of the bleeding cycle and the provocation of postmenopausal flowing. Therapy should be limited in its scope to a few months, and should not be prolonged for years.

Summary

A few of the significant endocrine contributions to obstetric and gynecologic thought and practice have been surveyed. It is not too much to hope that the next fifty years may bring many further endocrine solutions to physiologic, diagnostic, and therapeutic problems of our specialty. It may well be that the ultimate solution of eclamptic toxemia and genital carcinoma may be effected through the medium of an expanding knowledge of the endocrine system.

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HYSTERECTOMY

Therapeutic Necessity or Surgical Racket?

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WE HAVE gathered here to commemorate the Fiftieth Anniversary of the Chicago Lying-in Hospital, and to pay respect to the memory of its illustrious founder, Dr. Joseph B. DeLee. Devoted to the care of obstetric and gynecologic patients, and to the study of disease of the female reproductive organs, this citadel of the healing art has etched an enviable record in the history of obstetrics. The high aims and sound principles of its medical founder prospered and were further championed by the distinguished and indefatigable Dr. Fred L. Adair, who, with the aid of a capable staff, added new laurels to its record. Today, it is a source of satisfaction to know that, under the skillful and able leadership of Dr. William J. Dieckmann, the staff of the Chicago Lying-in Hospital stands well qualified to meet the challenge of fame as well as the growing responsibilities of medical care.

To all who played a part in the early organization and success of this great center goes well-deserved praise. To you, the men and women entrusted with its future, comes a just pride of hospital heritage and a challenge, for as you do so shall the record read, in your hands lies its destiny. May its coming glory reflect your own great success.

Since this hospital deals primarily with the functions of the female reproductive organs, it is fitting that we give some thought to the uterus and the indications for its extirpation. The role of this organ in obstetrics is well known. Its normal behavior during the nonpregnant state, especially during the menstrual cycle, is one of the more important revelations of our age. What, if any, its function may be during late middle age is still a matter for conjecture. That the uterus serves any useful purpose after its childbearing duty is over, is generally doubted. Its removal at this time is thought to cause no detraction in feminine economy. Indeed, extirpation purely as a measure of preventive medicine is by no means unheard of. The concept that uterine demand for estrogenic hormone may serve as a stimulator of ovarian activity and so play an important part in ovarian economy at a time when the sap of youth is running low has comparatively few adherents. The question of uteroovarian relationship is an important one, but until we learn more about the uterus as a consumer as well as a monitor of ovarian hormones, this question cannot be answered to everyone's satisfaction. While the existence or nonexistence of uterine function during middle age has an important bearing upon our subject matter, it does not alter the implications of the rather inelegant title of this paper. For few

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will deny that the health-restoring, and sometimes lifesaving, operation of hysterectomy is also subject to misuse and abuse. Even though future study fails to reveal an ovarian dependency upon uterine existence, hysterectomy in the absence of pelvic disease cannot be justified any more than can removal of the normal breast or gall bladder.

Since 1844, when Atlee probably first excised the uterus for myomas, the number of hysterectomies performed has been legion. Innumerable papers have been written upon the subject, many of which have contributed in a very real manner to our understanding of the indications, technique, therapeutic value, as well as hazards of the operation. Ever since the advent of hysterectomy, the progressive technical improvements of the operation based on increasing experience have been clearly recorded in the literature. Once a rare and spectacular procedure performed by only a few skilled and courageous surgeons, the operation today has become quite commonplace. Similarly, the indications, once highly restricted, have been so broadened as to warrant scrutiny and re-evaluation. No one can deny the importance of hysterectomy as a health-restoring and lifesaving measure, but one may question some of the present-day indications for its widespread performance. If enthusiasm for the operation has warped our judgment, it is not the first time this has happened. Ample precedent is to be found in the appendectomy and tonsillectomy "epidemics" of a few decades ago.

Medicine, like all scientific endeavor, is in a constant state of flux. The good of yesterday may be undesirable today. Progress, sometimes slow and imperceptible, has at other times been sudden and spectacular. What we have witnessed since the advent of the sulfonamides and penicillin may be only a forerunner of the tremendous influence to be exerted by chemotherapy in the future. That infection, one of the more common causes for surgical intervention, may soon come to occupy a secondary place is already foreshadowed by the dwindling disease of the Fallopian tube. Indeed, one need only contemplate what chemotherapy has accomplished in the management of gonorrhea, syphilis, and the pneumonias to realize that the time is rapidly approaching when many indications for surgery will have to be re-evaluated. Discovery of a specific chemotoxin for the tubercle bacillus, for example, might see the bottom drop out of the thoracic surgeon's collapse therapy. But chemotoxins are not the only levers of influence that warrant attention. Increasing knowledge concerning the hormones, the chemical regulators of the human body, has also affected surgery. Endoerinal uterine bleeding, one of the chief reasons for pelvic surgery, is partly solved, and the nonsurgical control of this troublesome symptom appears to be more than just a pipe dream.

Solomons¹ once stated, ". . . I would say a gynecologist is not a gynecologist until he ceases to perform unnecessary hysterectomies, for this operation has become nearly as overdone as the operations for tonsillectomy, appendectomy, and eutectage." The sentiment expressed by Solomons may well be heeded by all who perform the operation.

In order to learn something of the prevailing attitude regarding hysterectomy in communities both large and small, I undertook this somewhat unortho-

dox study based on 246 hysterectomies. If this number seems small when compared with numerically large series, I suggest you withhold judgment until I explain that they represent the hysterectomies performed during the first four months of 1945 in ten different hospitals, both large and small, in ten different communities, in three midwestern States. (There was one exeception: Hospital No. 5 covered a four months' period in 1944.) During the past few years I have made two attempts to accumulate data of the type here presented; the first through hospital pathologists, and the second through hospital directores, both of which resulted in failure. This, the third attempt, was suceessful because I obtained information where I should have sought it in the first place; namely, from the physieians themselves; a tribute to the cooperative spirit and seientific interest of Ameriean doetors.

This report differs from the usual statistical compilation in that it represents a sampling from large and small communities, and attempts correlation of symptoms and physieal findings with the histopathology actually observed.

TABLE I. NUMBER OF HYSTERECTOMIES ACCORDING TO AGE PERIOD

Age Period	Under 20	20-29	30-39	40-49	50-59	60-69	70-79
Number of Hysterectomies	1	30	78	108	22	6	1

Table I shows the number of hysterectomies aecording to age period. As antieipated, the majority were performed during the fourth and fifth decades, although no age period was entirely immune.

There were four postoperative deaths, a mortality rate of 1.6 per cent. This may be compared with a low of 0.6² per cent and a high of 4.64⁵ per cent reported in the literature.

TABLE II. TYPE AND NUMBER OF HYSTERECTOMIES PERFORMED IN EACH HOSPITAL STUDIED

Hospital	1	2	3	4	5	6	7	8	9	10	Total	Per cent
Subtotal	15	3	14	19	14	33	37	24	3	0	162	65.8
Total	12	0	0	16	27	6	4	2	1	4	72	29.2
Vaginal	2	0	0	1	0	2	2	0	0	5	12	4.8
Total for each hospital	29	3	14	36	41	41	43	26	4	9	246	99.8

Table II reveals a definite preferenee for the incomplete or subtotal exeision over the total by more than two to one. Since this study represents the work of many operators, this preponderance of the incomplete over the complete variety is interesting, if not entirely unexpected. In view of the enthusiasm and propaganda favoring the total operation, one might have expected a higher incidence for the complete extirpation. Apparently the general surgeon is not yet familiar with the frequently voiced desirability of the total operation, or else he is not impressed by the evidence so far presented. If the latter be the explanation, then I find it readily understandable. For, taking everything into eonsideration, the total operation is more difficult than the subtotal, opinions to the contrary notwithstanding. Furthermore, except for the obvious fact that future disease of the cervix is eliminated, the other advantages sometimes claimed for complete hysterectomy still remain to be proved. When hysterect-

tomy is necessary, I prefer the total operation for the specific and obvious advantage mentioned above. However, I am quite unimpressed by the evidence presuming to prove a lower mortality and morbidity for the total operation. Until thoroughly comparable cases treated by both methods have been evaluated, the benefits of total over the subtotal hysterectomy will remain a much discussed question with a single positive advantage—elimination of the cervix in favor of the total procedure. While this advantage seems real and sufficient enough to many of us, I question whether it justifies the potential added risk to the patient entailed by forcing total hysterectomy upon the occasional operator.

Table II was also prepared to show the number as well as type of operation for each hospital studied. For brevity's sake, and to prevent identification, subsequent tables have been condensed and the hospital numbers omitted.

TABLE III. CORRELATION BETWEEN AGE GROUP AND TYPE OF HYSTERECTOMY

Age period	Under 20	20-29	30-39	40-49	50-59	60-69	70-79	Totals
Subtotal	1	22	48	76	12	3	0	162
Total	0	8	29	26	8	0	1	72
Vaginal	0	0	1	6	2	3	0	12
Total No.	1	30	78	108	22	6	1	246

TABLE IV. COMPLAINTS OF PATIENTS

SYMPTOM.	NUMBER	PER CENT [*]
Bleeding	102	41.4
None given	43	17.4
Abdominal pain	24	9.7
Secondary { Nervousness Headaches Etc.	23	9.3
Pelvic pain	19	7.7
Pelvic mass	17	6.9
Backache	13	5.2
Bearing down and/or prolapse	11	4.4
Dysmenorrhea	10	4.0
Leucorrhea	9	3.6
Abdominal mass	6	2.8

*Percentages are based on 246 cases. Some patients, however, complained of more than one symptom.

Table III was prepared to determine whether concern over the cervical stump as a site for carcinoma in later life was reflected in a higher incidence of total hysterectomy in the older age groups. Apparently no such concern was evidenced, since during the fourth and fifth decades the subtotal operation still predominated.

The symptoms leading to medical care are shown in Table IV. It will be noted that bleeding heads the list. Other complaints included abdominal pain (9.7 per cent), pelvic pain (7.7 per cent), and backache (5.2 per cent). Almost 10 per cent (9.3 per cent) sought medical care for secondary symptoms. Under this heading are included fatigue, irritability, nervousness, and headache, complaints commonly listed as functional in character. Seventeen and four-tenths per cent had no complaints, an interesting observation, since most patients subjected to major surgery usually have a reason for seeking medical care. I do not

know whether this last figure is high or not, but doubtless the observation can be partly explained on the basis that routine pelvic examination revealed an asymptomatic condition for which operation was advisable.

TABLE V. FINDINGS ON PELVIC EXAMINATION.

FINDING	NUMBER	PER CENT*
Normal pelvis	46	18.6
Uterine fibroids	78	31.7
Enlarged uterus (fibrosis)	45	18.2
Pelvic inflammatory disease	17	6.9
Retrodisplacement	17	6.9
Relaxed pelvic floor	15	6.0
Prolapse	14	5.6
Cervix disease	13	5.2
Adhesions	13	5.2
Pelvic mass	12	4.8
Ovarian tumor	11	4.4
Carcinoma corpus	1	0.4
Polyps	2	0.8
Carcinoma cervix	1	0.4
Pregnancy	1	0.4
Ectopic	1	0.4
Bowel obstruction	1	0.4
Endometriosis	1	0.4
Degenerated area in uterus	1	0.4

*Based on 246 cases. Some, however, had more than one diagnosis on pelvic examination.

In Table V are listed the physical findings noted on digital examination. Since bleeding was the prominent symptom, it is not surprising to discover that uterine fibroids dominate the list of palpable diseases. However, the figure 31.7 per cent is somewhat deceptive, since many clinically suspected fibroids were later found to be either nonexistent or else extremely small. The significant observation in this cataloging of palpable findings is the fact that 18.6 per cent, almost one-fifth of all the women operated upon, were recorded as having no disease of the pelvic organs. This absence of palpable disease may, in part, be explained on the basis that the patient may have had troublesome symptoms, such as bleeding, without gross disease of the generative organs. Even so, this figure seems high.

In Table VI we have an analysis of the pathologist's findings. It is startling to note that 76, or 30.8 per cent, showed no histopathology of the organs removed. This figure is especially revealing, since included as acceptable pathology are disease of the adnexa, prolapse, hyperplasia of the endometrium, and relaxation. In other words, almost one-third of the patients in this series revealed no histologic evidence of disease. This astonishing figure warrants scrutiny. The facts that 17.4 per cent presented no symptoms, and 18.6 per cent had no palpable pelvic disease, do not of themselves permit the assumption that approximately one-fifth of the patients in this series had acute *remunerative* or *hip-pocket* hysterectomies. Some patients requiring surgery may have been unaware of the fact that they harbored a pelvic neoplasm, such as an ovarian or uterine tumor. Yet it was deemed feasible to remove such asymptomatic neoplasm. Similarly, patients may reveal no palpable disease

TABLE VI. PATHOLOGY OF ORGANS REMOVED

PATHOLOGY	NUMBER	PER CENT OF 246*
Fibroids	107	43.4
No pathology (or relaxation)	76	30.8
Endometrial hyperplasia	40	16.2
Salpingitis	32	13.0
Adenomyosis	23	9.3
Cervicitis	19	7.7
Polyps	16	6.5
Carcinoma (uterus or ovary)	13	5.2
Benign ovarian tumors	7	2.8
Endometriosis	7	2.8
Pregnancy (or retained products)	7	2.8
Myometrial hyperplasia	6	2.4
Fibrosis uteri	6	2.4
Prolapse	4	1.6

*Percentages are based on 246 cases, but in many instances more than one diagnosis was made.

of the pelvic viscera, and yet suffer considerably from blood loss due to the presence of hidden disease. In this category are such conditions as carcinoma, polyps, or hyperplasia of the endometrium. However, the bewildering discovery that 76, or 30.8 per cent, of the 246 patients operated upon were found to be free of pathology, is a stunning observation which cannot easily be accounted for. Since this report is based on a questionnaire study, it is possible that different interpretation of questions asked is reflected in the respective answers received by me. Error from this source is probably minimal, since the questionnaire was purposely simple and data on histopathology required only the copying of the pathologist's statement, all of which makes these observations more disconcerting.

TABLE VII. CORRELATION OF CASES WITHOUT HISTOPATHOLOGY AND NO SYMPTOMS AND/OR NO PALPABLE DISEASE

	NO SYMPTOMS		NO PALPABLE DISEASE		NEITHER SYMPTOMS NOR PALPABLE DISEASE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
No histopathology	42	17.1	45	18.7	41	16.6

Correlation of cases presenting no histopathology, no symptoms and/or normal pelvic findings is shown in Table VII. Seventeen and one-tenth per cent of patients had neither symptoms nor pathology of the removed organs, 18.7 per cent had neither palpable nor microscopic disease, while 16.6 per cent had neither symptoms, suspected disease on pelvic examination, nor microscopic evidence of disease in the removed organs.

TABLE VIII

	NUMBER	PER CENT
Clinical diagnosis confirmed by pathologist	122	49.6
Clinical diagnosis not confirmed, but operation justified	43	17.4
No histopathology (or relaxation)	76	30.8
Diagnosis contraindication to operation	5	2.0

In 49.7 per cent of patients operated upon, the clinical diagnosis was confirmed. In 17.4 per cent, the clinical diagnosis was not confirmed, but the operation nevertheless considered justifiable (Table VIII). In 33.1 per cent of the cases, there was either no disease, or else disease contraindicating hysterectomy, such as unsuspected pregnancy, infected retained secundines, etc.

Conclusion

The question asked in the title of this report may not be answerable on the basis of this study. But, if what we have observed in this look behind the scenes is confirmed by future studies, then we may be sure that when the curtain rises we shall witness a tragedy, painful and far-reaching in its implications.

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A NURSE LOOKS AHEAD*

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AT MEETINGS on obstetrics, it is quite in vogue nowadays to point with pride to the great reduction in the maternal death rate which has taken place during the past ten years. It is just as much in vogue to deplore the eight thousand maternal deaths which still occur in the United States every year, and to add that one-half of these deaths are needless, that these women are the very core of four thousand American families, and that deaths from puerperal causes are second in importance among women between the ages of 18 and 35 years.

I need not rehearse these facts with you, nor do I need to review the phenomenal advances which have been made in the science of obstetrics. You at the Chicago Lying-in Hospital, under the dynamic leadership of Dr. DeLee, and now of Dr. Dieckmann and Dr. Davis, and a long line of nurses, have contributed much toward the perfection of the medical and nursing techniques which have reduced the deaths of women from childbirth causes to the present low rate.

These advances are almost entirely based on the prevention, detection, and treatment of disease, abnormality, and complication. The death rate from toxemia has been halved in ten years. Infection, in good maternity services, has lost its terror. Hemorrhage, under the best conditions, no longer needs to sap the vital life forces of mothers. Infertility can be overcome. Prematurity, erythroblastosis, and a long list of other hazards are beginning to respond to scientific knowledge and treatment. Pelvis can be measured to the very last centimeter, and the best method of delivery can be chosen well in advance.

The average expectant mother comes to the doctor without having known him previously. How she selects him depends upon her intelligence, her knowledge about medical care, the supply of doctors in her community, and her income. Before marriage she has had little or no preparation for marriage and the coming of children. Her store of information about babies, how they are born and how they grow, about family planning, about the psychological hurdles in her family life when babies come, is composed of a curious mixture of sense and nonsense, science and superstition.

She comes to her doctor expecting a thorough physical going-over, probably her first in many years. Therefore she comes in trepidation. What *will* the doctor find wrong with her? Her blood pressure goes up and she has palpitation of the heart as she waits to see him. The questions with which the doctor opens the interview are based on her past bouts with disease—the scarlet fever she had at eight, the measles and mumps at twelve, followed by a trip to the hospital with appendicitis and the cause of death of her father and mother, or, if now living, the diseases with which they are afflicted.

*Address delivered at the Fiftieth Anniversary celebration of the Chicago Lying-in Hospital, Oct. 29, 1915.

Armed with this strictly pathologic knowledge, the doctor proceeds to a pathologic examination. When he has finished, he issues some orders, non-committally writes out a prescription, and tells her to come back next month with a specimen of urine in her handbag.

The same approach to the patient prevails in the maternity clinics—with their benches of waiting women; where privacy is ignored; where the contacts with the doctor are so often answers to questions about bowel movements, headaches, spots before the eyes, and tests for syphilis and anemia and the like. Then, donning an unbecoming gown, she crawls upon a table to be measured and poked while the clerk or intern or medical student makes note of the ununderstandable (to her) findings dictated by the doctor.

Nursing care, as an adjunct to medical care, falls into the same attitude toward the patient, who is frequently looked upon as a "case," rather than a person with an individuality all her own, a member of a family of people, with desires, fears, hopes, and a common background. The interest of doctors and nurses in a "case" frequently mounts in proportion to the pathology encountered.

The patient returns home from her first interview a bit dishevelled in dress and coiffure, and more disturbed in mind and spirit. She has received the best obstetric care that can be obtained. It is care which makes her conscious of her body, rather than her whole personality. It is care which will watch her blood pressure, her blood count, her weight, her kidney function; will keep close track of her baby's development, month by month; and be prepared to provide every scientific safeguard when she goes into labor.

But this obstetric care is not designed for the woman's peace of mind, nor for teaching her facts which she should know about her health, her baby, and her marital and family relations. To be sure, it gives the doctor a comprehensive view of his patient for disaster prevention and for her safety at all times. The expectant mother, herself, gets little out of it which will help her to live a fuller, more healthful life. In fact, this care which puts its chief emphasis on the body and its functions, on menstruation, respiration, circulation, and elimination, can put an effective damper on the inner radiance which came upon her when she first knew that she was expecting a baby.

The system, at best, bows only slightly to the need for teaching mothers the facts which will make the coming of their babies a joy to them and their husbands. Many doctors look askance at efforts to teach expectant parents, perhaps believing that a little knowledge is a dangerous thing. The attitude almost seems to be—keep them ignorant and they will obey orders better.

This attitude among doctors is illustrated by the small number of women referred to our Maternity Center Association's classes for expectant mothers. During the past four years, nearly 5,000 mothers came to class, and less than 10 per cent were referred by doctors, and those by only a few doctors.

The emphasis on pathology in obstetric care is not only deeply imbedded in the thinking of the medical and nursing professions. It is part of the folkways of every nation. Our language, for instance, has five times as many words for sickness as for health. In the Netherlands, prenatal clinics are called

"searching clinics"—that is, they search for abnormalities. Does freedom from evident symptoms of disease cause many women not to register for care until the seventh or eighth month of pregnancy, or to put off seeing the doctor for the first time until they are actually in labor? Have they not taken for granted that they needed the doctor only if they were ill? Is not this same attitude toward pathology in obstetric care evident in community unwillingness to provide good maternity facilities for those who cannot pay for their own care? Why else were nearly 200,000 women permitted to have their babies last year in the United States without any care whatsoever, before, during, and after labor, and hundreds of thousands more given a kind of care which would make the staff of an institution with standards such as this shudder with dismay?

Looking at maternity care largely in terms of preventing or curing pathologic conditions, important as all this is, has tended to make of obstetrics a service unrelated to all that has gone before or may come after. I believe that we are reaching the maximum point of progress which can be achieved, no matter how many more scientific medical discoveries are made in the future, nor how high is the *technical* excellence of medical and nursing care and of hospital management.

We must have more than just the expansion of this kind of obstetric care to every nook and cranny of the country. We have come to the point in obstetrics when we need a new philosophical concept of the aims and goals toward which we are striving. The whole emphasis must be shifted from the negative to the positive, from pathology to health, from the reproductive organs to the woman, the mother, the wife, if we are to avoid the inevitable slowing down of progress by the age-old principle of diminishing returns.

The coming of a baby into a family is more than a physical process governed only by biologic chemistry and limited to the science of drugs, masks, routines, and methods. Maternity is not a separate experience in life, unrelated to the rest of life. The coming of a baby has roots in all that goes before. It is the culmination of life processes. It is not one isolated person having a baby in an isolated moment of time, but is the result of the inheritance of mother and father, of how they grew up, of what they are in body, mind, and spirit, of what they know about marriage, marital relations, family planning, about healthful living and nutrition, about budgeting time and money, about the growth of the baby from the moment of fertilization, and how pregnancy tests the mother's spirit as well as her body. Outside influences matter, too—relationships with in-laws, opportunities for recreation, economic status, the community in which the expectant parents live and its facilities for good maternity care.

In this new concept of obstetrics, the control of pathology during pregnancy, labor, and the puerperium becomes only one factor in a well-integrated plan for maternity care. Health is not sought merely for health's sake, but rather that each member of the family may get the most out of living. The good health of the whole family is the first secret of strong family life. Living together is most fun when everybody is well. So a new mother, under this positive philosophy, would do everything in her power to stay well, for the sake of her baby, her husband, and herself. She would see the doctor just as soon

as she thinks she is pregnant. The doctor would be more than an eagle-eyed Sherlock Holmes, poking here and there only for clues to something wrong. He and the nurse become friendly advisers who work out with the mother and father the prescription for their healthful living during pregnancy and afterward.

The examination, then, is no pathologic inspection of parts. Cases are metamorphosed into people. Obstetrics is no emergency service, but a part of the care and guidance which a person needs from childhood through adolescence into adulthood to make each major adjustment to life, from the baffling days of puberty through the satisfactions of parenthood, the strains of menopause, and finally to the satisfactions as well as the aches of grandparenthood. Under such a scheme, the doctor and the parents know and work on the assumption that the kind of baby a mother and father have is closely related to the kind of babies, children, adolescents, and adults they were and are themselves. Under such a scheme, the doctor, nurse, health officer, educator, and parent work together.

Already there are signs that obstetrics is being related to all that goes before in the life of both parents. One practical evidence of change is the development of group medical practice. Under this system, we find a growing integration of the efforts of the obstetrician, the pediatrician, the internist, the surgeon, and the other specialists. If group practice were logically developed, a person could receive integrated medical care and instruction from infancy, through childhood, adolescence, until he or she becomes a parent and afterward. Sociomedical histories, instead of being scattered all over the lot as they are now under group practice, would be complete in one file and readily available, and also readily transferable. But group practice can achieve only best results if it broadens its concepts of obstetric care from the pathologic to the normal, from disease to health. We can talk all we want about socialized medicine, health insurance, and the thousand and one other schemes that are now being propounded to provide medical care to all, but none of these schemes can begin to meet the need unless all of medical care is integrated and woven together, and until the negative, pathologic viewpoint is integrated into the positive, health-seeking viewpoint.

The average doctor looks askance at expanding the concept of obstetric care to the realm of teaching positive facts, perhaps because such ideas were entirely lacking in his medical training. The responsibility for teaching the basic facts, however, is not alone his. It is a function of the school. That function has been almost ignored in present-day education. In a few isolated instances, some experiments of teaching young people a few isolated facts have been carried on. But the dead hand of traditional unwillingness to face the issue squarely with young people is laid over most of our educational system. Even so-called progressive private schools are backward when it comes to teaching anything but bees, birds, and butterflies to their students. The way to learn about human reproduction is not in the gutter, but in a course in biology. The place to learn about family relationships and their importance is in the home and in courses in sociology, history, English, and kindred subjects. When, and only when,

young people are taught these basic facts of living and live them out in their own lives, will the positive viewpoint toward obstetrics win the battle in the medical profession, in nursing, in hospital care.

I see these changes coming—obstetrics will be related to all of medical care from infancy to old age; the emphasis will shift from pathology to health; the basic facts which make for strong families will be taught in school and college. I see these changes coming because parents will demand them. The time of accepting blindly a substandard of medical care is gone already. Parents are beginning to choose their doctors with wisdom. Doctors are being talked about more than ever before. Mothers are not looking for a handsome doctor, nor do they go to a physician just because he is a fraternity brother of Uncle George. They want good care! And many understand what constitutes good care.

Frequently professional people feel that they stand above the common herd, that their activities are unrelated to the laws of the market place, of supply and demand, of selling a product that fills a need and meets a demand. Evidence of this attitude is to be found in the growing regimentation in our clinic and hospital services which results in mass treatment and losing sight of the individual patient, in direct contradiction to the high-sounding phrases of democracy and the rights of the individual which were our battle slogans. Nurses are being trained under these circumstances, which are undermining at the very beginning the cooperative relationship between the doctor and the nurse and the patient. The medical and nursing professions and hospital management cannot much longer stand aloof and provide the type of care which *they* think is good for the hoi polloi. Therefore, I see a change coming in obstetric practice, caused primarily by a change in ideas about obstetric care among expectant parents. This change will come gradually, but surely.

Now where does the nurse fit into this changing picture of obstetrics? The rank and file of nurses are not prepared to play their parts in this coming new phase of maternity care. With a few exceptions, they were not well prepared for their part in the present scheme of things. They have not been well taught in the art and science of obstetrics. The average nurse-training course gives the nurse only a nodding acquaintance with obstetrics and the streamlined war-time courses gave even less. The average basic nurse-training courses are so weak in obstetrics that advanced obstetric nursing courses cannot be added to the present curricula because there is not an adequate foundation on which to build.

Nurses can only play an important role in the future broadening concept of obstetrics if they are well prepared. Nursing schools in the main are adjuncts of hospitals. They operate on a shoestring, with inadequate budgets and too few well-trained instructors overworked to the point where they cannot do their best. Because of these financial stringencies, the students are exploited. Primarily they do the work of the hospital, their studies are secondary. Post-graduate nursing students frequently complain that they are only taught different methods for doing the same things they learned as undergraduates with little science and few principles. In spite of this lack of good graduate

courses in obstetric nursing, across this land in the last few decades have risen self-taught leaders with courage, knowledge, and ability to take their place with the best-qualified obstetricians.

Medical schools, on the other hand, are educational institutions, often well endowed and well staffed. Education is the first priority. The hospital is the laboratory, as it should be. Yet it takes years of hospital residence in obstetrics to transform the graduate of the medical school into a budding obstetric specialist. I wonder *why* we have been content to permit this vast difference in the quality of the preparation of the two workers whose work is so interdependent? Good care of patients, including education, research, administration of services, and even the best opportunities for education of the physician, is as dependent on a high grade of nursing as on a high grade of medicine. A poor grade of nursing drags medical standards down just as a poor grade of medicine drags the quality of nursing down. While nursing education puts its chief emphasis on the generalized nurse, shall we say the jack-of-all-trades but master of none, medical education was tending to make of the doctor a master of one specialty. This gap between the quality of preparation of doctor and nurse gives them little common ground on which to meet, even at the bedside of the patient. This, of course, is reflected in patient care. The time was when doctor and nurse worked so closely together over each patient that the patient was always conscious of "my doctor" and "my nurse." Today, with rare exceptions, the patient has no close relationship with a particular nurse and, if she goes to a clinic, no close relationship with a particular doctor or nurse, so the nurse and doctor alike have no particular interest in a particular patient.

This close relationship has disappeared, and as yet no satisfactory substitute has appeared on the scene. Too often maternity patients today see so many people—the clerk, the registrar, the technician, the nurse, the doctor, the social worker, another nurse, another doctor—that the patient is practically the only one who can summarize the case.

This situation cannot continue if nursing is to take its rightful place in the coming scheme of things designed to promote the health of the people. But I know nurses. I have seen their driving spirit accomplish results that were considered impossible. The present situation of the nurse is the result of years of imperceptible change. She is taught to keep her eye on the patient, on the events of the moment. This she has done, to the neglect of her own position in the sociomedical scheme of things. This change in her position has occurred unnoticed. When it is brought to her attention, I am confident that she will rise to the challenge and create for herself, as did Florence Nightingale in another generation, a new place in the world of medicine and health.

As I look ahead, I see the breaking down of the hard line which has been drawn between medicine and nursing. I see the teamwork of the doctor and nurse established on a new basis, with the goal of good service to each patient looming larger day by day. This new basis will be a division of labor, according to who is best able to provide a particular service for the patient, and not according to a protocol whose chief goal is to protect the best interest of doctor, hospital, or nurse.

This new basis will be possible because nurse training will be so vastly improved that nurses will be professionally equipped to share on all levels the responsibilities of good care. This better education of nurses will come about when schools of nursing decide to operate only where ideal hospital and public health services justify their use for educational purposes.

I see the time coming when advanced courses in the specialties will be organized in our university schools, where only students with special interests and aptitudes will be admitted. The graduates will then be clinical specialists. When these specialists are paid according to their knowledge and ability, and when nursing organizations recognize these specialists, draw up qualifications, develop a plan for their certification, and provide some channel for their continued professional expression and growth, then there will be nurses qualified to work with medical specialists.

The beginning has been made in our field of obstetrics in the courses in nurse-midwifery or advanced maternity nursing—call it what you will. But the financial burden of developing these courses has fallen upon private agencies with limited resources. Just before and during the war, some Government money became available for the training of obstetric nurses, but the stipends granted have not begun to cover the cost of the complete education. I see the day coming when these courses will be recognized as so important that they will be put upon a sound financial basis and become an integral part of our university schools.

Public education will continue to play an important role. The time is coming when expectant parents will be taught to buy care at what it actually costs and not on the cost-minus or the cost-plus basis at which it is sold today, that is, with the patient paying only part of the cost, the rest being underwritten by private benefactions, public funds, or by some people paying much more than their share. When that time comes, highly qualified obstetricians and highly qualified obstetric nurses will fit naturally into the picture, for the costs of this specialized service can be met because the people are willing to pay for it. The resulting higher economic level for these specialists will attract more competent doctors and nurses into the practice of obstetrics.

At the same time I see an educated public unwilling longer to permit highly qualified people to do work which can be done by those less skilled. Look at the medical and nursing time both in and out of hospitals today that is spent doing odd jobs that almost anyone could do.

I see, too, qualified experts in the schools of nursing teaching biology, human reproduction, human relations, marriage, and all that has to do with family living. I see nurses learning the gentle art of helping people to live together on the spiritual as well as the physical plane, not competing with the skills of other workers, but rather, complementing these skills. I see doctors and nurses learning to make better use of teaching aids developed by specialists in health education—with posters to brighten clinic walls; leaflets on helpful subjects taking the place of 1938 magazines on doctors' waiting-room tables; movies in the schools; radio talks; exhibits at county fairs.

The day of the closed corporation in medical care is vanishing—with the obstetrician treating his patients as if the months of pregnancy and the few weeks after were all that mattered; with the pediatrician looking upon those little patients of his as if they were separate entities isolated from their families; with the nurse tending only to her knitting in the domain of nursing; with the health officer dealing with his vital statistics as if those pie charts of his were objects, not people; with the educator ruling which of the facts of human life can be taught to young people and which must be censored.

The time is coming when each highly developed skill will be woven together for the well-being of each person in the community like the threads of needle-point, each in its place, separate, yet forming a pattern. The doctor will be concerned with nursing, with education, with public health, with hospital management. The nurse will be concerned with medical care, education, hospital management, and all other community activities and interests which are closely related to the lives of her patients. So it will be with the health officer, the educator, the civic-minded community leader, the hospital manager.

Thus, in the days when all the world is made one, will we find that all of life is one, and that oneness is centered in people, their rights, their privileges, their well-being, their health and happiness. This is the ultimate goal of medicine and nursing—and it can be achieved if we have the inspiration, imagination, and determination to see it through.

654 MADISON AVENUE

Original Communications

THE SIGNIFICANCE OF MYOMA UTERI IN PREGNANCY

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THE occurrence of myoma uteri in pregnancy is generally considered to be associated with an increased incidence of certain complications. Many articles have been written which stress the frequency of sterility, abortion, abnormal presentation, prolonged labor, dystocia, hemorrhage, and morbidity. This study includes all of the cases of pregnancy complicated by myoma uteri in the Woman's Clinic of the New York Hospital during the seven-year period between Jan. 1, 1937, and Dec. 31, 1943. There were 361 cases of myoma uteri in 22,283 pregnancies.

The total incidence of myoma uteri in this series is 1.4 per cent. If abortions are excluded, the incidence is lowered to 1.3 per cent. This figure is in close agreement with that of many other authors. However, since many small myomas are not readily detectable, it is probable that the actual figure is somewhat greater.

We feel that the complications caused by myomas during pregnancy might be better evaluated if some consideration were given to their size. In general, the obstetrician gives little thought to small myomas, or overlooks them completely. Nevertheless, we have included in this series all myomas which have been described in relation to pregnancy. For purposes of evaluation, we will compare large and small myomas in separate groups. We have arbitrarily considered myomas 6 cm. or more in diameter as large or significant, and those less than 6 cm. in diameter as small or insignificant. It is very likely that position and location of the myoma in the uterine wall are of as much or more importance than the size of the myoma, but the latter is much easier to evaluate in the pregnant or postpartum uterus. The chief reason that a diameter of 6 cm. was considered a criterion of significant myomas was the relationship of myomas of this size to dystocia. Dystocia due to myomas is one important complication of pregnancy which cannot be disputed. In this series, no myoma less than 6 cm. caused any difficulty during delivery, and in the majority of cases where obstruction was encountered, the myomas were larger. We feel that by comparing the group of large and small myomas found among these patients, the role of the myoma in producing complications during pregnancy can be clarified. Of the 361 patients with myomas, 110, or over 30 per cent. had myomas 6 cm. in diameter or larger.

It is well known that fibroids are a complication more frequently found in the late childbearing age. As would be expected, the average age of the myomatous patient was 33 years, or ten years older than the optimum age for

childbearing. One hundred fifty-eight, or 43 per cent, of all cases, were 35 years of age or older. Fifty-seven, or 15.7 per cent, were elderly primigravidas as contrasted with the clinic incidence of elderly primigravida, which is 2.98 per cent. Age itself is a factor which must be taken into consideration in evaluating the complications and operative interference which has been found among the present series.

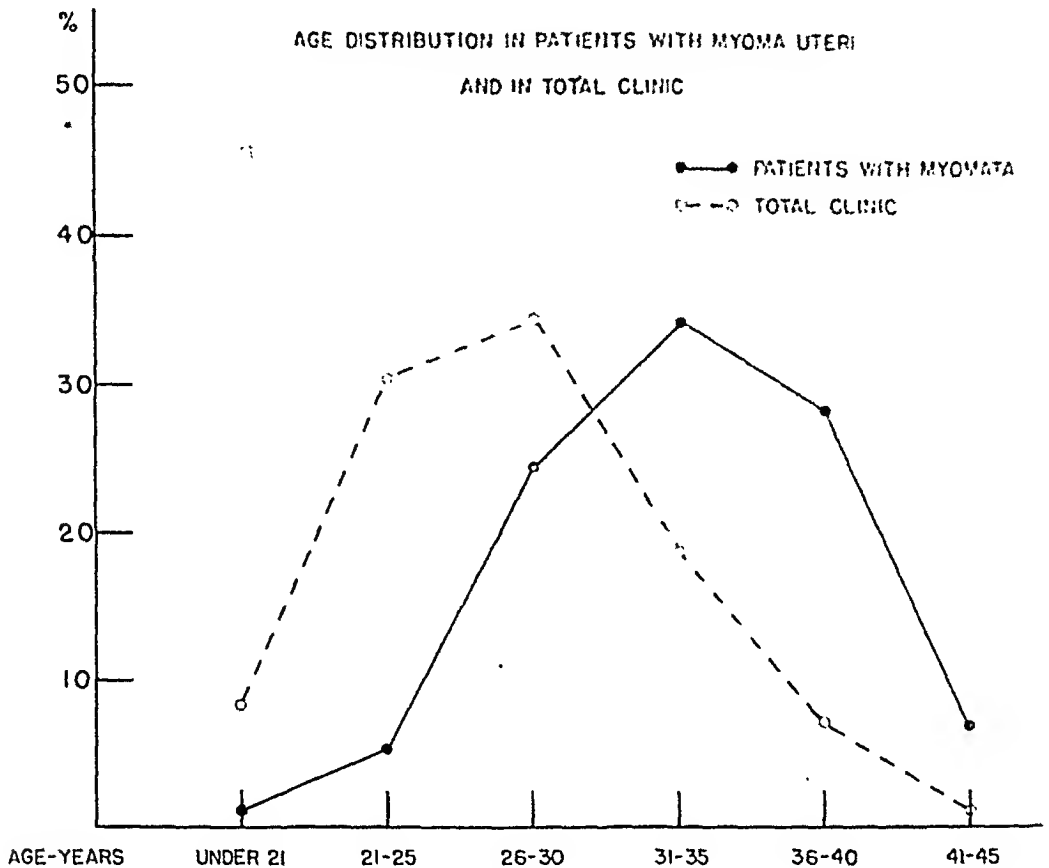


FIG. 1.

In direct relationship to this older age group, there was an increased incidence of toxemia. This was the most frequent complication among these patients with myoma, and it occurred in 15.4 per cent or twice the clinic incidence of 7.8 per cent.

Sterility among patients with myoma is very difficult to evaluate. It is generally quoted as occurring in 30 per cent of the women with fibroids, in contrast to 15 per cent of an unselected female population. We can make no pretense of evaluating this problem with the material which is available in this study. Certainly, it seems reasonable to suppose that in cases where the fibroid encroaches on the endometrial cavity, where there is an associated endometritis or endometrial hyperplasia, that sterility would result. However, there are many factors causing sterility which are not recognized. Too frequently the clinician is tempted to make the fibroid uterus the solution to his problem. It is well to remind ourselves that the fibroid is more apt to be present in the late childbearing age. A sterile woman with fibroids at 35 years of age may

have had none at 25 years of age when sterility was first present, but had not become manifest. It is during the first half of the childbearing period that a woman is most apt to become pregnant, but later, as the likelihood of pregnancy becomes somewhat less, the tendency toward the development of fibroids becomes more pronounced. Table I is presented to show that infertility is not apparent among the 160 primigravidas in this series. Contraceptive measures which may have been used by these patients are not known. The occurrence of relative infertility among patients with large and small myomas did not differ significantly.

TABLE I. RELATIVE FERTILITY OF 160 PRIMIGRAVIDAS

Years married	1-3 yr.	4-5 yr.	6-8 yr.	9+ yr.
Number of patients	102	26	16	16

Data pertinent to myoma uteri were revealed by the past histories of approximately 10 per cent of the patients in this study. In the entire group, nine had had a previous myomeetomy, and 33 had noted changes in their menses from six months to several years preceding the present pregnancy. Thirty of the patients told of profuse periods lasting 6 to 12 days, two noted frequent periods occurring 14 to 21 days, and one had intermenstrual staining. However, there was no significant difference in the course or termination of pregnancy of these patients giving a history of menstrual irregularity. Of the nine who had had a previous myomeetomy, pregnancy terminated by abortion in four, cesarean section in three, and breech extraction in one. There was only one full-term spontaneous delivery.

Unfortunately, in many patients, myoma uteri is overlooked during the course of pregnancy. At times, myomas were first discovered when pain, abortion, hemorrhage, or cesarean section focused attention on them. Myomas can best be evaluated when the uterus is nearest its nonpregnant state. As the uterus grows, the fibroids may become inaccessible or alter their shape, owing to relative changes in position or axis. They are often confused with fetal parts and are not readily outlined. This difficulty is well illustrated in our series, which shows that most fibroids are detected in the first trimester or post partum (see Table II).

TABLE II. TIME MYOMAS WERE FIRST NOTED IN PREGNANCY

	ENTIRE GROUP	GROUP WITH LARGE MYOMAS
1st trimester	37.4%	57.5%
2nd trimester	10.6%	15.1%
3rd trimester	8.4%	15.1%
Delivery	5.0%	8.8%
Post partum	38.7%	4.4%

The larger the myoma, the more readily it is detected; but even among the significant group, there were a number which were not found until attention was directed to them at delivery. Doubtless, in some instances, myomas discovered at term became significant because of their increase in size during pregnancy. Growth of the myoma during pregnancy was very difficult to

follow for reasons that we have already stated. In many cases, a myoma noted in early pregnancy could not be outlined later on. In a few instances, the myomas were noted to have increased to twice their original size.

Pain is a symptom not infrequently associated with myomas in the rapidly growing pregnant uterus. It was present in 40 cases, or 11 per cent of the entire series, and was somewhat more prominent among the group of significant myomas where it occurred in 15.6 per cent. In approximately half of the cases it offered no problem, for it was not persistent, and once the nature of the trouble was explained to the patient, she was reassured and needed no treatment. In about 50 per cent, however, it was of sufficient degree to require hospitalization for observation or treatment. A hysterectomy was performed in four cases during the first trimester. In most cases, the acute symptoms are relieved after a few days of bed rest, so that, on the whole, our policy is conservative. Recent studies have shown that myomectomy during pregnancy carried a high fetal mortality and an increased maternal risk. We believe it should be avoided wherever possible. No myomectomies were performed during pregnancy because of pain, and we have found no occasion to regret our choice. Pain in itself had little relationship to the complications of pregnancy occurring among this group. However, two cesarean sections were performed where pain appeared to be a factor. These patients had had pain throughout their pregnancy, and a myomectomy was done at the time of operation. Strangely enough, postpartum pain was present in none of these patients who complained of pain during their antepartum course.

Abortion has been mentioned by many authors as occurring more frequently in the myomatous patient. In this series, there were 63 abortions which occurred among 361 pregnancies, an incidence of 17.1 per cent. This figure is compared with the general clinic incidence of abortions which was 8 per cent during the same period of time. The incidence of abortion among patients with significant myomas was 22.9 per cent, which is somewhat higher than it was for the group as a whole. However, among this group there was an increased operative incidence (hysterectomy, myomectomy), but when only spontaneous abortions are considered, the difference is not as marked. This would seem to indicate that the number and location of the tumors, as well as size, are important factors predisposing to abortion.

In further support of a relationship between myoma and an increased incidence of abortions, we find among 1,651 consecutive abortions occurring in

TABLE III. TYPES OF ABORTION

Spontaneous abortion	16
Incomplete abortion	29
Abortion with hysterectomy	7
Abortion with hysterectomy with special indications	10
Pain	4
Pain and incarceration	1
Ectopic	3
Therapeutic (hypertension and chronic nephritis)	2
Criminal	1
Total	63

this clinic, the incidence of myoma uteri was 3.8 per cent, in contrast to an incidence of 1.3 per cent myoma uteri in the viable pregnancy group. It would appear that the incidence of abortion is twice as frequent in patients with myoma as in the average clinic group. This observation is supported by the past histories of the patients we are studying. If we exclude from consideration 13 patients who admitted induced abortions, we find that 28 per cent of the patients in this study had one or more abortions. This is a higher incidence than that which is generally reported by our patients.

Corresponding with an increased incidence of abortion, there is also an increased incidence of premature labor among patients with myomas. While our general clinic average of prematurity is approximately 2.5 per cent, in this group it is 5 per cent. The tendency toward prematurity is somewhat greater among those with significant myomas, the incidence being 8.2 per cent. Among the premature deliveries in this clinic, myomas were noted in 3.3 per cent, a frequency similar to that found in the abortion group.

In those pregnancies progressing to viability, there was a notable increase in abnormal presentation. Of 298 pregnancies, vertex presentation occurred in only 90.6 per cent. Breech presentation was found in 6.7 per cent, which is similar to its incidence in the elderly primigravida (7 per cent). This percentage is definitely higher than that of the general clinic where the incidence is 4.7 per cent. There was no significant difference in the occurrence of the breech presentation between patients with large or small myomas. The four transverse presentations occurred in the group with large myomas where the size or location of the tumors could readily interfere with the normal presentation.

TABLE IV. PRESENTATION

PRESENTATION	SIGNIFICANT	INSIGNIFICANT	TOTAL GROUP
Vertex	72	198	270 (90.6%)
Breech	9	11	20 (6.7%)
Transverse	4	0	4 (1.3%)
Twins			4 (1.3%)

It has generally been asserted throughout the literature that myoma uteri is responsible for uterine inertia and prolonged labor. A high incidence of premature rupture of the membranes is also reported. The average duration of labor among our patients who delivered vaginally was 10.8 hours in the multipara, and 18.9 hours in the primipara. Prolonged labor, defined as lasting 30 hours or more, occurred in 9.1 per cent of the entire series, while precipitate labor, three hours or less, occurred in 6.1 per cent. These figures show no change in the duration of labor over those in the general clinic, where the corresponding figures were found to be 9.1 per cent for prolonged labor and 6.1 per cent for precipitate labor. Furthermore, there was no increased tendency toward long labors among patients with significant myomas. Among the patients in this group who delivered vaginally, 6.4 per cent were reported as having prolonged labor, while 4.5 per cent delivered in three hours or less. Premature rupture of the membranes occurred in 17.3 per cent of the entire series, although the general clinic incidence of 36.1 per cent is much higher.

We have found no evidence that myoma uteri per se has been a factor in uterine inertia, and we are unable to agree with those authors who stress the high incidence of premature rupture of the membranes and prolonged labor as important complications of pregnancy in patients with myomas.

TABLE V. TYPE OF DELIVERY OF PATIENTS WITH MYOMAS

	LARGE	SMALL	ENTIRE GROUP
Spontaneous	45	163	208
Operative	40	50	90
Cesarean section	23	17	40
Classical	8	7	
Classical and myomectomy	3	2	
Cervical	5	4	
Cervical and myomectomy	1	1	
Radical	6	2	
Low forceps	7	14	21
Breech	5	8	13
Mid forceps	2	2	4
Dührssen's	6	3	3
Version-extraction	2	1	3
Removal of placenta	1	2	3
Other*	0	3	3

*Tamponade, bag induction, impacted shoulders disengaged with Braun hook.

From Table V, we see that there is an increased incidence of operative deliveries, particularly with respect to cesarean sections among obstetric patients with myoma. The incidence of cesarean section among patients with myomas was 13.4 per cent, or more than five times our average clinic incidence of 2.4 per cent. It was performed in 27 per cent of patients with large myomas in contrast to 8.4 per cent of those with small myomas. The indications for section in both groups are compared in Table VI.

TABLE VI. INDICATIONS FOR CESAREAN SECTION

	GROUP WITH LARGE MYOMA	GROUP WITH SMALL MYOMA	ENTIRE SERIES
Dystocia due to myoma	10	0	10
Painful or degenerating myomas	1	1	2
Elderly primipara with myoma	2	1	3
Disproportion	2	5	7
Elderly primipara with sterility	2	1	3
Elderly primipara with poor labor	1	1	2
Previous section or previous myomectomy	2	1	3
Elderly primipara with breech	1	1	2
Eclampsia or severe pre-eclampsia	2	1	3
Elderly primipara with hypertension	0	1	1
Premature separation of placenta	0	2	2
Elderly primipara with contracted pelvis	0	1	1
Chronic nephritis	0	1	1
Total	23	17	40

In 6 per cent of all deliveries, or 21 per cent of the operative deliveries, operation was performed with myoma uteri as one of the primary indications. It is in the method of delivery that patients with significant or insignificant myomas appear in greatest contrast. The operative incidence among patients

with large myomas was twice as high (47 per cent) as those with small myomas (23.4 per cent) where the operative incidence is similar to that of the general clinic (24.3 per cent). In 16 cases, or 40 per cent, of the operative deliveries in those with significant fibroids, myoma was the chief indication, while in only 2, or 6 per cent, of the insignificant ones was it an important consideration. Both patients in the latter group had cesarean sections, the indications being elderly primigravida with myoma in one, and painful or degenerating myoma in the other. In both cases, we feel that more conservative management would have been preferable. Among the former group of patients with large myomas, two were delivered by version and extraction, one by mid-forceps and thirteen by cesarean section. Among the patients who were delivered by cesarean section, the indications were elderly primipara with myoma, 2; painful fibroids, 1; and dystocia due to myoma, 10.

The cases in which myoma uteri caused mechanical difficulties are of special interest. Of these patients, eight were primiparas, and five were multiparas. Twelve patients went to term, and one patient was aborted at ten weeks by a hysterectomy because of pain and incarceration of the tumor in the pelvis. Most of the tumors were located in the lower uterine segment. Two of the tumors were under the symphysis on the anterior portion of the cervix, four were in the lower right uterine segment, four were in the lower posterior uterus, and two in the right anterior uterus and adnexal region. The myomas were multiple, but the size of the prominent tumors were estimated in seven patients to be 6 to 8 cm. in diameter; in three, 10 to 12 cm.; and in two, 15 to 20 cm. Eight of the myomas were noted in the first trimester, two in the second, and two at delivery or in labor. None of these patients gave evidence of having symptoms related to myoma prior to pregnancy. The antepartum course of those who went to term was uneventful, save for moderate pain and tenderness noted over the myomas in two patients. Abnormal presentations in this group were striking. There were four transverse, three breech, and five vertex presentations. Delivery, of course, was operative. There were two version extractions, and ten cesarean sections. Seven of the sections were elective, while three were indicated after a trial of labor of from 3 to 25 hours. Myomectomy was performed at the time of cesarean section in two patients, and hysterectomy in another two. The myomas were not recognized in two patients until disproportion became evident during labor. In one of the patients, delivery was accomplished by version-extraction and craniotomy, while in the other, a low flap cesarean operation was done after 25 hours of labor without engagement of the head. There were three fetal deaths. Two of them were caused by intraeranian hemorrhage following version and extraction, and one was attributed to asphyxia following a 25-hour labor during which the myoma caused an unrecognized obstruction to delivery.

As we found little evidence of uterine atony during labor, so there does not seem to be an increased tendency for the uterus to relax post partum, thereby increasing bleeding during the third stage and following delivery. The average blood loss for the 258 vaginal deliveries was 200 c.c. At this clinic a separate note is dictated following postpartum hemorrhage which

describes the third stage, probable cause and amount of blood lost. A postpartum hemorrhage is defined as a blood loss equivalent to 1 per cent of the body weight or 600 c.c. or more (cesarean sections are not included). Ten patients in this series had a postpartum hemorrhage. In five patients, the blood loss was measured between 600 and 900 c.c.; in two it was measured between 1,000 and 1,499 c.c.; and in three, it was estimated at 1,500 c.c. or more. The incidence of hemorrhage was 3.8 per cent, while in the total clinic, the yearly incidence of hemorrhage varied from 1.7 per cent to 4.4 per cent during the same period of time.

TABLE VII. POSTPARTUM HEMORRHAGE IN PATIENTS WITH MYOMA UTERI

CAUSE	BLOOD LOSS	TYPE OF DELIVERY	INDICATION FOR DELIVERY	DURATION OF LABOR	SIZE OF MYOMA
Uterine atony	1,500+ c.c.	Spontaneous		16 25/60	Small, irregular on posterior uterus
Cervical and perineal lacerations	1,500 c.c.	Midforceps with Dührssen's incisions	Maternal distress	66 51/60	3 cm. anterior fundus
Premature separation of placenta	1,500 c.c.	Spontaneous		9 18/60	3 cm. anterior fundus
Uterine atony and incomplete separation of the placenta	1,020 c.c.	Spontaneous		6	6.8 cm. in fundus
Uterine atony and incomplete separation of the placenta	1,200 c.c.	Low forceps	Lack of progress in 2nd stage	13 15/60	Several large in both sides of fundus
Lateral sulcus tears	800 c.c.	Low forceps	Lack of progress	18 55/60	8 cm.
Uterine atony*	700 c.c.	Spontaneous		10 1/60	3 x 4 cm. pedunculated
Retained placenta in the cervix	700 c.c.	FTO manual removal	Retained placenta	5 44/60	Small, anterior wall
Incomplete separation of the placenta	600 c.c.	Breech extraction	Breech	16 48/60	2 cm. left cornua
Uterine atony	600 c.c.	Breech extraction	Breech	13 26/60	5.6 cm. submucous

*Fibroid noted in 3rd trimester.

Hemorrhage followed operative delivery in six patients and occurred after spontaneous delivery in four (see Table VII). It occurred in six patients with small myomas and in four patients with myomas between 6 and 8 cm. in diameter. The hemorrhages were attributed to incomplete separation of the placenta in two of the cases, cervical or vaginal lacerations in two others, and premature separation of the placenta in another. In the remaining five cases, it was ascribed to uterine atony, although in two there was an associated incomplete separation of the placenta. There was one maternal death. The most profuse hemorrhage occurred in patients having myomas from 1 to 3 cm. in diameter. It is significant that with but one exception, when the fibroid was noted in the third trimester, none of the myomas were discovered until

after delivery. Myomas not readily recognized during normal pregnancies are often discovered after careful evaluation when abnormalities occur. This tendency is well illustrated by the following case:

A 31-year-old para i gravida iii, with a history of postpartum hemorrhage, registered in the twelfth week of her pregnancy. Her antepartum course was normal. At term, she was delivered of a 2,760 Gm. infant after 16 hours of labor. The placenta was expressed in one minute, accompanied by 150 c.c. of blood. Although the fundus appeared to contract well at first, it did not remain firm, and moderate bleeding continued. At the end of an hour there was an estimated blood loss of 850 c.c. During the next 7 hours, the uterus was packed twice and the patient received several transfusions. The total blood loss was estimated between 2,000 and 3,000 c.c., and attributed to atony in a fibroid uterus. Clot retraction and fragility at the time of hemorrhage were somewhat impaired, but were essentially normal when repeated later. A small irregularity was palpated on the posterior aspect of the fundus at the time of hemorrhage, but the presence of the fibroid was not confirmed at the time of the sixth week postpartum examination.

Of the hemorrhages occurring in patients with large myomas, one was caused by a lateral sulcus tear, two were associated with uterine atony and incomplete separation of the placenta, and one with uterine atony alone. We feel that the latter case is one of the very rare instances in which myoma uteri may contribute to hemorrhage. It is reported as follows:

The patient was a 29-year-old primigravida who registered in the fourteenth week of her pregnancy, and whose antepartum course was normal. The membranes ruptured prematurely 13 hours prior to the onset of labor. After 13 hours of labor, she was delivered by breech extraction. The placenta was expressed one minute later, accompanied by an estimated blood loss of 300 c.c. The fundus was boggy and the bleeding profuse during the repair of the episiotomy. After intravenous pitocin, the uterus contracted well and bleeding ceased. The measured blood loss attributed to uterine atony was 600 c.c. This patient gave evidence of an intrauterine infection at the time of delivery and afterwards developed daily temperatures ranging from 39° to 40° C. Involution was poor and the lochia profuse. On her thirty-fifth postpartum day, inspection of the cervix revealed a necrotic myoma 5 to 6 cm. in diameter protruding through the cervical os. A myomectomy was performed.

TABLE VIII. INCIDENCE OF PUERPERAL SEPSIS IN PATIENTS WITH MYOMAS

	SIGNIFICANT MYOMAS	INSIGNIFICANT MYOMAS	WHOLE GROUP
Abortion	28 %	13.1%	19 %
Spontaneous delivery	8.8% }	3 % }	4.3% }
Operative delivery	51.1% }	28 % }	41.1% }
	31.7%	6.8%	15.4%

The incidence of puerperal infection among patients with myomas is high (Table VIII). It was 15.8 per cent in this group, including abortions. Puerperal infection is defined as a temperature of 38° C. or over on any two successive days (i.e., over 24 hours), but excluding the day of delivery, where the rise in temperature cannot be attributed to extragenital infections. The puerperal morbidity which includes two-day fevers from all causes, including puerperal infections, was not significantly higher. Among patients with myomas, the incidence of puerperal infections was over twice as high as the incidence among patients in the clinic, which is 6 per cent. To a large extent, this can be attributed to the unusually large number of operative deliveries

which occurred in this group. Among those with spontaneous deliveries, the incidence of puerperal sepsis is 4.3 per cent, in contrast to an incidence of 41.1 per cent which is found in the operative group. However, there is a considerable difference in morbidity in those with large and small myomas, which cannot be entirely explained by the method of delivery. Puerperal sepsis occurred in 31.7 per cent of the patients with myomas over 6 cm. By analyzing these figures, the tendency toward a higher incidence of infection among significant myomas is emphasized. In spontaneous deliveries, infection occurred in 8.8 per cent of patients with large myomas, compared with 3 per cent of patients with small ones. In operative deliveries, infection occurred in 51 per cent of patients with large myomas and in 28 per cent of those with small myomas. Even among abortions, the morbidity in the two groups was different. The total incidence of puerperal infection in abortions was 19 per cent. In patients with large myomas it was 28 per cent, as compared with 13 per cent in patients with small ones. We do not believe that the high percentage of infection can be explained entirely on the basis of the frequent operative interference found in this group, but agree with those authors who believe that the myomatous uterus is more susceptible to infection than the normal ones.

Aside from fever, the puerperium of this group of patients was also complicated by several operative procedures. Two vaginal myomectomies were performed, one after an eight-week abortion, the other after full-term delivery. Both of these patients had submucous myomas 6 to 8 cm. in diameter, which were infected and bleeding. An abdominal myomectomy was performed on the seventh postpartum day on a patient who complained of intense pain over a large myoma (20 cm.) in the fundus. Three patients returned 3 to 5 weeks post partum, because of bleeding and a curettage was done. The pathologic diagnosis in two was "retained products of conception," and in the other, "myometritis." In the latter case submucous fibroids were felt on curettage. This patient has since had another uneventful delivery which was followed by the same difficulty. Three patients returned 4 to 6 weeks following abortion or premature delivery for elective surgery. Two subtotal hysterectomies and one myomectomy and suspension were done at this time. With the exception of those who had curettage, all of the operations occurred in patients with large myomas.

TABLE IX. FETAL MORTALITY 9.6%

	LARGE MYOMAS		SMALL MYOMAS		ENTIRE SERIES
Deadborn	5	} -10.5%	13	} -9.2%	18
Stillborn, heart audible, no respirations	0		3		3
Neonatal	4		4		8

In 302 viable births there were 29 infant deaths, giving an infantile mortality rate of 9.6 per cent. This is more than two times that of the general clinic (3.7 per cent), but is not out of proportion to the high infant mortality rate reported in the literature among patients with myomas. Approximately one-third of the deaths occurred in prematures and the other two-thirds in

full-term infants. As shown in Table IX, there were 18 deadborn, 3 stillbirths, and 8 neonatal deaths. Among the neonatal deaths, prematurity and intracranial hemorrhage were chiefly responsible; among stillbirths, asphyxia. Of the deadborn infants, nine deaths occurred before labor. Premature separation of the placenta in one and maternal diabetes in two cases were probably responsible for three deaths, but in six the cause was not known. The other nine died during complications of labor and delivery. One death occurred during a prolonged labor of 92 hours, two during difficult operative deliveries with Dührssen's incisions, two during version-extraction (one with craniotomy). Prolapse of the cord in a breech presentation caused another death. The fetal hearts were lost during labor in a patient with hydramnios (twins) and in another at the time of section. The cause of death was not explained in either case. Myoma uteri was undoubtedly a factor in the two deaths following version and extraction, as it offered definite obstruction to delivery; and, as we have shown, it may have been a precipitating factor in some of the deaths from prematurity.

There were three maternal deaths, giving a maternal mortality rate of 0.87 per cent. Two deaths from generalized peritonitis and sepsis followed cesarean section. One of them occurred in a 42-year-old primigravida who had a classical cesarean section at term, 10 hours after rupture of the membranes, and before the onset of labor. She had several large fibroids measuring 6 to 9 cm. in diameter in the right cornua and lower uterine segment. The other death followed cesarean section and hysterectomy which was performed in the thirty-fourth week of pregnancy because of chronic nephritis. Hysterectomy was selected as a means of sterilization because of the presence of several small pedunculated and intramural fibroids. The third death was caused by hemorrhage and obstetric shock. The patient was delivered of a 3,420 gram infant through a 7 cm. dilated cervix by means of a Dührssen's incision and midforceps; the indication was maternal exhaustion after nearly 67 hours of labor. A constriction ring was present at the time of delivery. There was an estimated blood loss of 1,500 c.c., largely due to lacerations in the cervix and vagina. When the patient failed to respond adequately to treatment for shock, a laparotomy was performed. No retroperitoneal hemorrhage was found, but a small 3 cm. myoma was noted on the anterior fundus. The patient expired shortly after operation. Certainly the presence of the myoma had little relationship to the cause of death in the last two cases.

Discussion

Myoma uteri is an important complication of pregnancy, but we do not agree that it is responsible for an increased incidence of postpartum hemorrhage and prolonged labor which have been stressed in the literature as important considerations in the patient with fibroids. It is known that uterine inertia is more apt to be found in the elderly gravid woman where the fibroid is also more frequent. However, it is at times when abnormalities occur that the obstetrician is only too glad to explain his difficulties by the most tangible evidence at hand. We should like to point out to further substantiate our opinion that extensive studies made in this clinic on prolonged labor and hemorrhage fail to indict the fibroid on either charge. We do have evidence of an unequivocal relationship of the fibroid uterus to abortion and prematurity which occur over twice as frequently among patients with myomas. Dystocia is an undisputed and serious complication, especially when it is not recognized in early labor. However, we may add that many myomas which

are thought to offer difficulty before term will rise from the lower pelvis with the rapidly growing uterus and give no trouble at delivery. One important complication of the fibroid in pregnancy which we believe is not generally appreciated is an increased incidence of puerperal sepsis in the presence of large myomas. This should seriously be considered before undertaking any major operative procedures upon these patients. The elderly primigravida with myomas should not constitute an indication for cesarean section per se unless other abnormalities exist or there is definite dystocia caused by the myoma. Because of the high incidence of elderly primigravidas among patients with myomas, we feel that in the past some of the problems associated with this group of patients have been confused with that of the patients with myomas. In conclusion, we feel that, wherever it is possible, the conservative management of the pregnant woman with fibroids will prove the best policy.

Summary .

1. The incidence of myoma uteri among the obstetric patients at this clinic is 1.4 per cent.

2. The role of myoma uteri in causing complications of pregnancy is clarified by comparing the patients who had myomas over 6 cm. in diameter to patients with myomas that were less than 6 cm. in diameter.

3. Since myoma uteri are more frequently found in the late childbearing ages, there is a high incidence of elderly primigravidas (15.7 per cent).

4. The significance of myoma uteri in causing sterility is difficult to evaluate.

5. Myomas are more readily detected in early pregnancy or postpartum when the entire surface of the uterus can be explored on bimanual examination. Frequently they are only discovered when complications of pregnancy and delivery focus attention on them.

6. Antepartum pain due to myoma was present in 11 per cent of the patients in this series. However, there were very few cases where pain was severe enough to necessitate operative intervention.

7. The incidence of abortion (17.1 per cent) and premature labor (5 per cent) in this series was twice the clinic incidence, which is 8 per cent and 2.5 per cent, respectively.

8. Presentation is affected only by large tumors which interfere with the adaptation of the fetus to the longitudinal axis of the uterus.

9. There is no evidence that myoma uteri is a factor in causing prolonged labor or premature rupture of the membranes.

10. There is a high operative incidence among patients with large myomas (47 per cent) compared with patients with small fibroids (23.4 per cent) who have an incidence of operative deliveries similar to the general clinic.

11. Thirteen patients had definite dystocia due to myoma.

12. Postpartum hemorrhage is rarely caused by myomas. The incidence of postpartum hemorrhage among these patients was 3.8 per cent; an incidence similar to that found in the total clinic, which varied from 1.7 per cent to 4.4 per cent during the same period of time.

13. The incidence of puerperal sepsis was 15.8 per cent, or over twice as high as we find among the general clinic population. The increase in morbidity occurs almost entirely in the group of patients with large myomas. However, it cannot be accounted for on the basis of an increased operative incidence in this group as it is also proportionately higher following abortion and spontaneous delivery.

14. The fetal mortality among patients in this series is 9.6 per cent compared with that of the clinic, which is 3.46 per cent.

15. There were three maternal deaths. The presence of myomas was incidental and entirely unrelated to the cause of death in two of the patients.

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LUTEOMA OF THE OVARY

A Case Showing Decidualization of the Endometrium and a High Pregnanediol Excretion Rate

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THERE is a rare tumor of the ovary which is associated with amenorrhea, hirsutism, hypertrophy of the clitoris, and a diabetic type of glucose tolerance curve. It is grossly characterized by the yellow color seen on cross section. It has been called "luteoma," "luteoblastoma," "hypernephroma of the ovary," "adrenal cortical carcinoma of ovarian origin," "yellow tumor of the ovary," "luteinized granulosa-cell tumor," "adrenal-like ovarian tumor," "virilizing lipoid-cell tumor of the ovary," and "masculinovoblastoma."^{1,2} Kepler, Dockerty, and Priestley³ have recently collected and reviewed the literature and list fourteen cases, including one of their own, as authentic.

The chief discussion centering about this tumor is not a disagreement as to the clinical picture it produces or its course, but rather what its origin is and what the correct name of it should be. The most popular hypothesis seems to be that most of these tumors are of ectopic adrenal origin. The terms "luteoma" or "luteinoma" are frowned upon by recent authors, though one of the early writers on this subject, Glynn,⁴ had come to the conclusion that they were of corpus luteum origin.

The following case report of such a tumor occurring in a young Italian girl of 15 years may throw some light on the physiologic nature of such tumors, and strengthen the idea that they may be functionally closely related to the corpus luteum.

Case Report

The patient, a rather heavy-set brunette of 15 years, 5 feet, 5½ inches tall, weighing 134 pounds, had been troubled at the age of 6 years with a tumor of the left upper thigh in the region of the greater trochanter. The tumor was said to measure 8 by 8 by 4 cm., and was surgically removed at the New York Skin and Cancer Hospital by Dr. Robert H. Kennedy. Microscopic sections were diagnosed as "central chondroma" at that time. Recent x-rays have suggested the diagnosis of "fibrous dysplasia." The tumor, or its surgical excision, resulted in a permanent deformity of the left leg, characterized by shortening, and a decrease in the size of the entire limb. The patient walked with a decided limp.

The patient's menstrual periods began at 11 years of age, and recurred every twenty-eight days, lasting four to five days. The flow was usually rather scanty. She had slight dysmenorrhea. Her periods stopped abruptly when she was fourteen years old, a year before she came to the hospital, and did not recur preoperatively. Accompanying the amenorrhea, the patient noticed a gradual increase of 10 pounds in weight, a deepening or hoarseness of her voice, and a well-marked increase in axillary and pubic hair, with a spread of the latter up onto the lower abdomen. There was no evidence of growth of hair on the face. It was noted that there had been no change in mental attitude and that the quality of her work in school was good. She had been promoted regularly with the other girls in her class.

On physical examination the general bodily configuration was feminine, but there was a heaviness of the shoulders and a prominence of the upper thoracic spine suggesting the so-called "buffalo hump" type of deformity. The face and upper chest were covered with numerous acneform red papules. The legs were unusually hairy. The pubic escutcheon was masculine in outline. The breasts were well formed with large areolae, about the margins

of which were numerous coarse black hairs. The face was rather full and heavy. There was a slight black mustache, but no beard. There were no striae. The shortening and decrease in diameter of the left leg as a result of the tumor of the left femur were obvious. The patient's voice was low-pitched and rather hoarse.

The heart was not enlarged to percussion, and the sounds were normal. No murmurs were heard. The blood pressure was 140/70. The lungs were clear to percussion and auscultation.

No abdominal masses could be felt. On pelvic examination the clitoris was noticeably enlarged. The vagina admitted one finger or a small speculum, exposing a normal vaginal cervix. The fundus was anterior, movable, and normal in size. Behind the fundus, approximately in the midline, was a solid ovarian tumor which seemed to be about 8 cm. in diameter. This tumor could be felt easily on rectal examination also. The impression was gained that the tumor arose in the left ovary.

Thinking that the most likely diagnosis in this case was an arrhenoblastoma of the left ovary, we admitted her to the wards of the Memorial Hospital for a period of intensive study preoperatively. At the end of two weeks the patient complained of epigastric abdominal pain, dizziness, nausea, and finally she vomited. A sudden rise in temperature to 101° F., and pulse to 100, were noted. Pelvic examination showed the tumor to have increased rapidly in size, so that it was thought to be about three times as large as when she was first examined. The tumor felt fixed. In view of this evidence of growth it was decided to delay no longer, but operate at once.

Consequently, on the next morning under gas-oxygen-ether anesthesia the abdomen was opened in the midline, and a freely movable well-encapsulated smooth tumor of the left ovary, measuring about 15 cm. in diameter, was removed along with the left tube. The operation was easily and quickly performed. The uterus and right ovary appeared normal and were not disturbed. The patient made an entirely uncomplicated postoperative recovery and was discharged on the thirteenth postoperative day.

The laparotomy was preceded by an examination under anesthesia and by a curettage. This was done chiefly to obtain a specimen of the endometrium, since we were not aware of the endometrial picture which might accompany an arrhenoblastoma.

Laboratory Data.—The urine was normal. Specific gravity varied from 1.012 to 1.024. No albumin or sugar was found on repeated examination. The sediment was negative.

The red blood count was 4,450,000 to 4,610,000; hemoglobin, 90 to 95 per cent; and hematocrit, 38.5 per cent preoperatively. The white blood count varied from 6,100 to 12,300. The differential was normal.

The serum bilirubin was 2.2 mg. and 1.5 mg. per 100 c.c. preoperatively.

Serum chlorides were 107 milliequivalents per liter. Serum cholesterol was determined on two occasions preoperatively. The total amount was 150.5 mg. and 127.5 mg. per 100 c.c., of which 42.7 mg. and 45.6 mg. were reported as esters.

The serum protein was 7.2 per cent. The blood urea nitrogen was 41 mg. per 100 c.c.

The basal metabolic rate was -3.

A glucose tolerance curve was of interest in that it showed the delayed fall mentioned as characteristic of this type of tumor.³ The fasting blood sugar level was 86.6 mg., rising to 176.2 mg. one-half hour after administration of glucose. At one hour, it was 159.4; at two hours, 148.1; and at three hours, 102.6.

Pathology.—Grossly the tumor was a smooth oval mass, 16 by 13½ by 8 cm., with a glistening, somewhat bluish capsule. On section the appearance was quite striking (Fig. 1), the main mass of tissue being grayish and somewhat gelatinous in consistency, interspersed with areas of dark red hemorrhage. Here and there were irregular masses of yellow tissue with somewhat wavy or corrugated outlines, somewhat suggestive of the wavy pattern of the normal corpus luteum. Numerous vessels throughout the mass showed adherent thrombi, and it was thought that the rapid increase in size of the tumor noted clinically was probably the result of this thrombosis and subsequent edema.

On microscopic examination the grayish gelatinous areas of the tumor were found to be composed of polygonal or elongated cells embedded in a loose edematous collagenous stroma

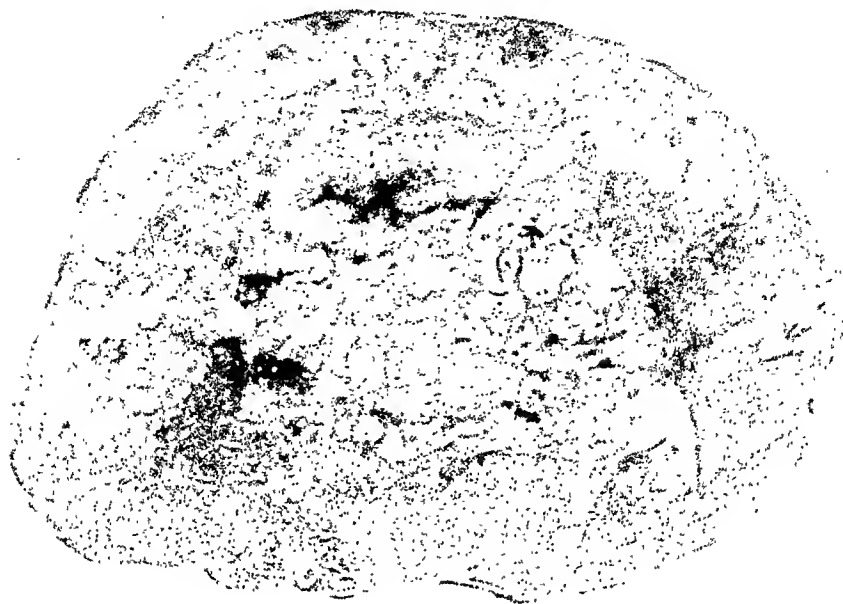


FIG. 1.

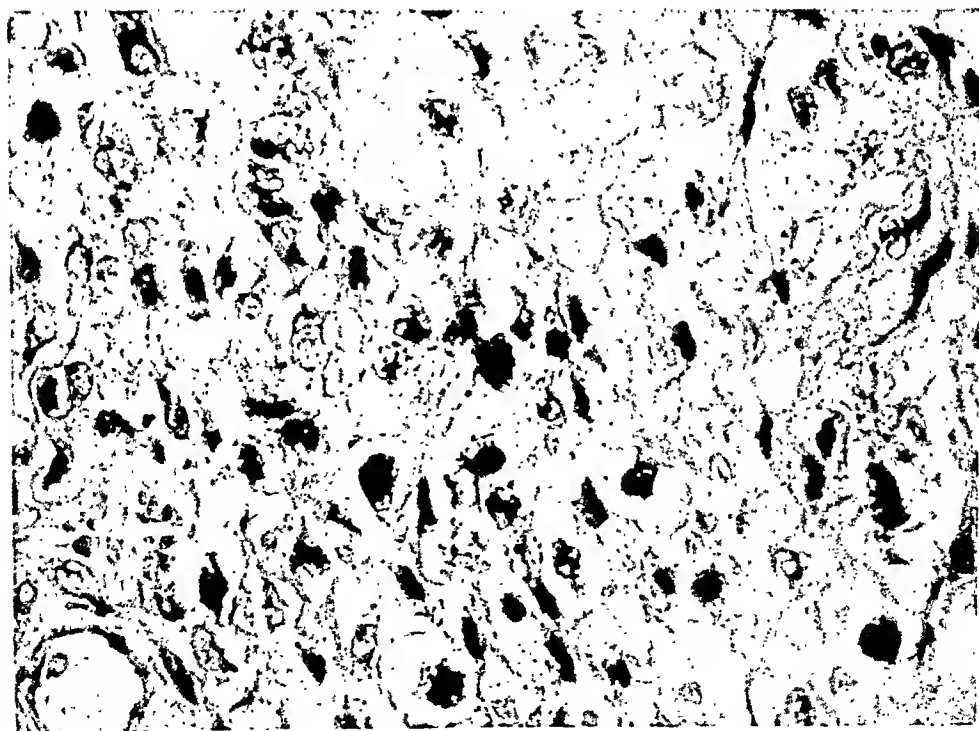


FIG. 2.

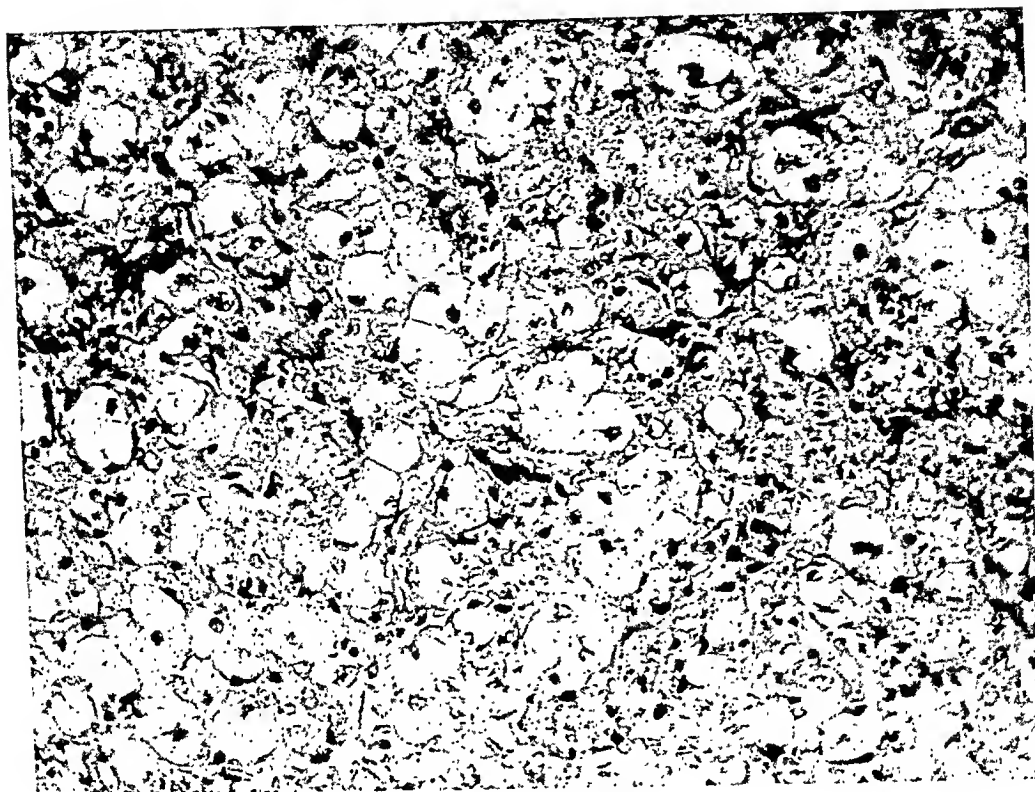


Fig. 3.

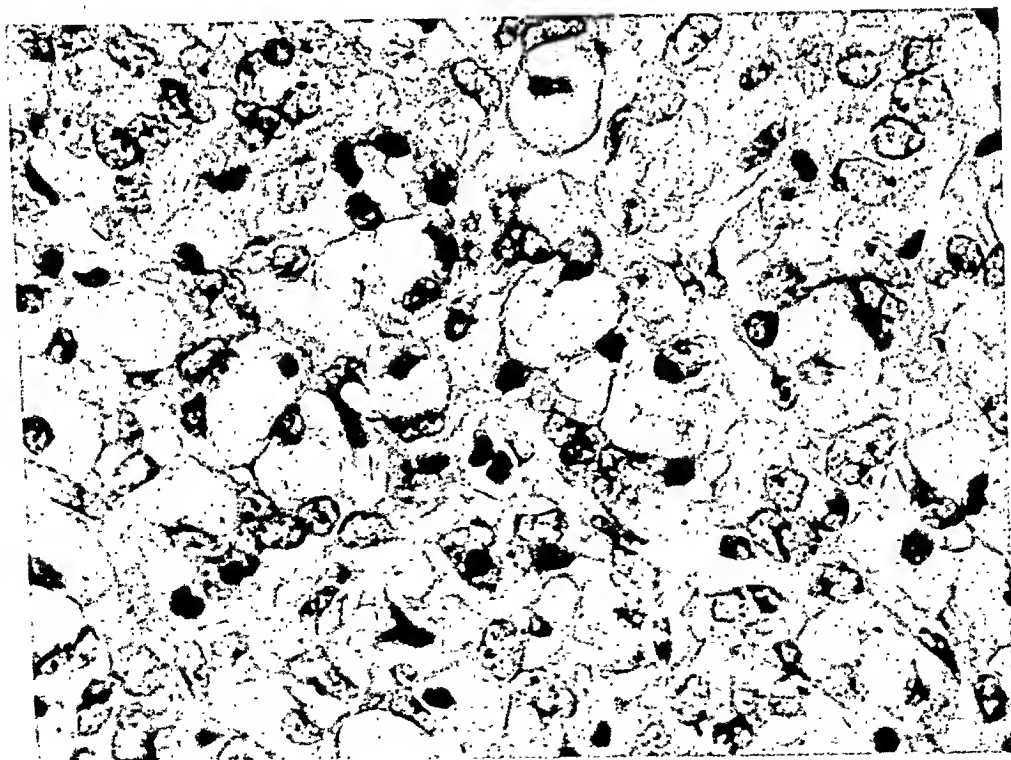


Fig. 4.

(Fig. 2). The cells had fairly large nuclei, each of which contained a large nucleolus. In some areas the tissue was quite cellular, and the collagenous stroma dense. In other areas the stroma was very thin and lightly stained, while the cells took on the appearance of embryonic fibroblasts such as one sees in the edge of a growing tissue culture. The contrast between cell body and stroma was seen best with Masson's trichrome stain.

When the yellowish areas were examined it was found that in them the cells were distorted by the presence of large vacuoles in the cytoplasm (Figs. 3 and 4). The nuclei of these cells were more vesicular than in the grayish areas. There was much less collagenous stroma. The vacuoles, when examined with the aid of a fat stain, were found to be filled by globules of fat (Fig. 5). It was noted that the cellular outlines of these fat-filled cells were not particularly sharp and distinct, but often seemed to blend into one another so that frequently one could not tell to which nucleus a given fat globule belonged.

The entire tumor was rather vascular, numerous thin-walled vessels being seen throughout and occasional areas of interstitial hemorrhage. No mitotic figures were seen in any of the nuclei, and this fact, together with the evident edema and interstitial hemorrhage, again suggested the impression gained from the gross appearance of the tumor that its sudden increase in size was a vascular phenomenon rather than being due to true tumor growth.

A very interesting finding was the almost complete decidualization of the endometrium (Fig. 6). Almost every cell beneath the surface epithelium was swollen with a sharp distinct cell wall, while the endometrial glands seemed few and far between.

Subsequent Course.—Following her operation the patient had a normal five-day menstrual period beginning on the thirty-eighth postoperative day and, since that time two and one-half years ago, she has continued to menstruate regularly and normally approximately every thirty days. The acne slowly disappeared. The patient thinks there is some decrease in hairiness, but this is not very marked. No change in the size of the clitoris or the hoarseness of the voice has been noted.

Three weeks after her operation the patient was admitted again to the hospital for laboratory study. There were no changes in the urinalysis or routine blood counts. Hematocrit readings were 37 per cent, as compared with 38.5 per cent preoperatively.

The serum bilirubin was 1.5 mg.; calcium, 10.4 mg.; chlorides, 102; serum cholesterol, 131.8, of which 87.9 were esters. These findings are all essentially unchanged from the preoperative levels. The alkaline phosphatase was 3.8 Bodansky units. The phosphorus was 4.12 mg. per 100 c.c. Serum protein was 7.5 per cent and blood urea nitrogen 7.9 mg. per 100 c.c. The basal metabolic rate was -3, the same value as was found preoperatively.

The only noteworthy change was in the glucose tolerance curve, which had previously been diabetic in type and was now normal. The values found were 81.3 mg. per 100 c.c. in the fasting sample; 165 mg. at one-half hour; 148.6 mg. at one hour; 90 mg. at two hours, and 66 mg. at three hours.

Hormone Findings.—We were under the impression that this patient was suffering from a masculinizing arrhenoblastoma. Consequently careful urine collections were made and assayed preoperatively for 17-ketosteroids. Table I gives the complete figures. These show a daily output preoperatively of about 21 mg. androsterone equivalent as measured by the Callow modification of the Zimmerman reaction⁵ or approximately double the normal excretion rate for women in our experience. For twenty-four hours postoperatively the excretion rate remained high. It fell then to an average of 9.3 mg. androsterone equivalent per twenty-four hours, or less than half the preoperative levels. The highest daily postoperative rate was 14.7 mg. equivalent, the lowest 4.4 mg. androsterone equivalent. Since our attention was concentrated on supposed "male" hormone output, only two three-day specimens of urine were assayed for estrogens. This was done using castrated female mice as previously described.⁶ The first assay showed 89 mouse units per day (8.9 γ estrone equivalent), the second 147 mouse units (14.7 γ estrone equivalent). One postoperative determination showed a fall in estrogens to 15 mouse units or 1.5 γ estrone equivalent. The normal woman during the course of a monthly cycle will vary greatly in her estrogenic excretion rate. Consequently, the above figures might be within normal range. However, they do show that the patient's amenorrhea was not due to an ovarian failure to excrete estrogens. In our laboratory the

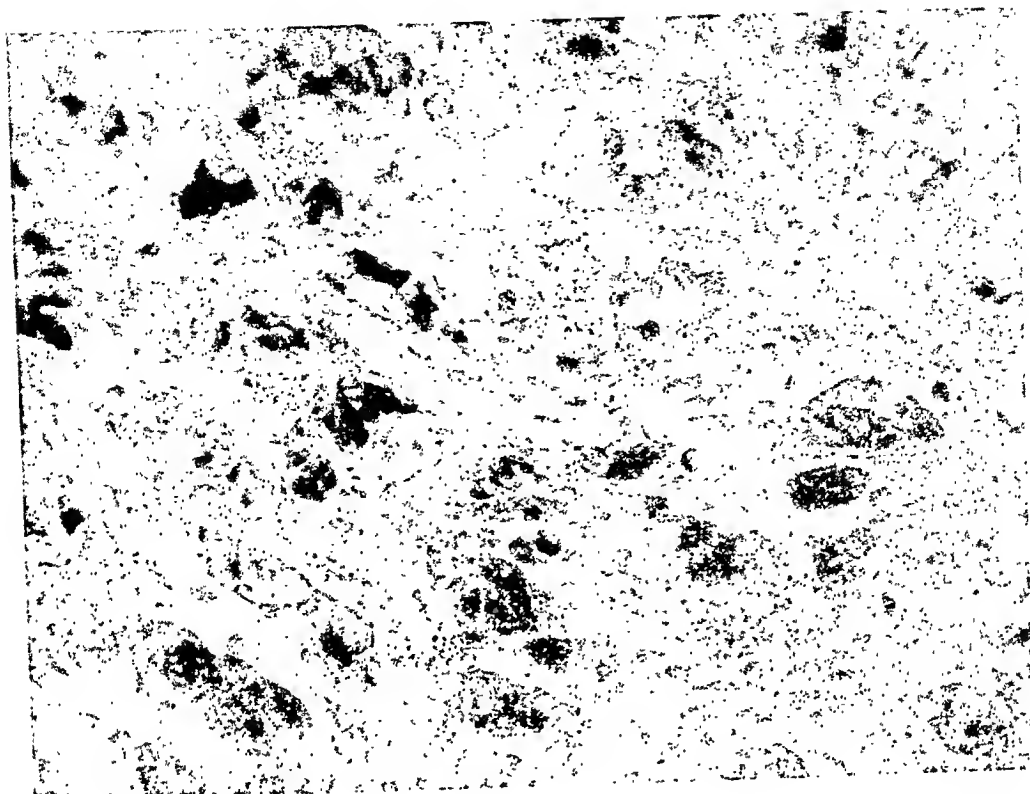


Fig. 5.

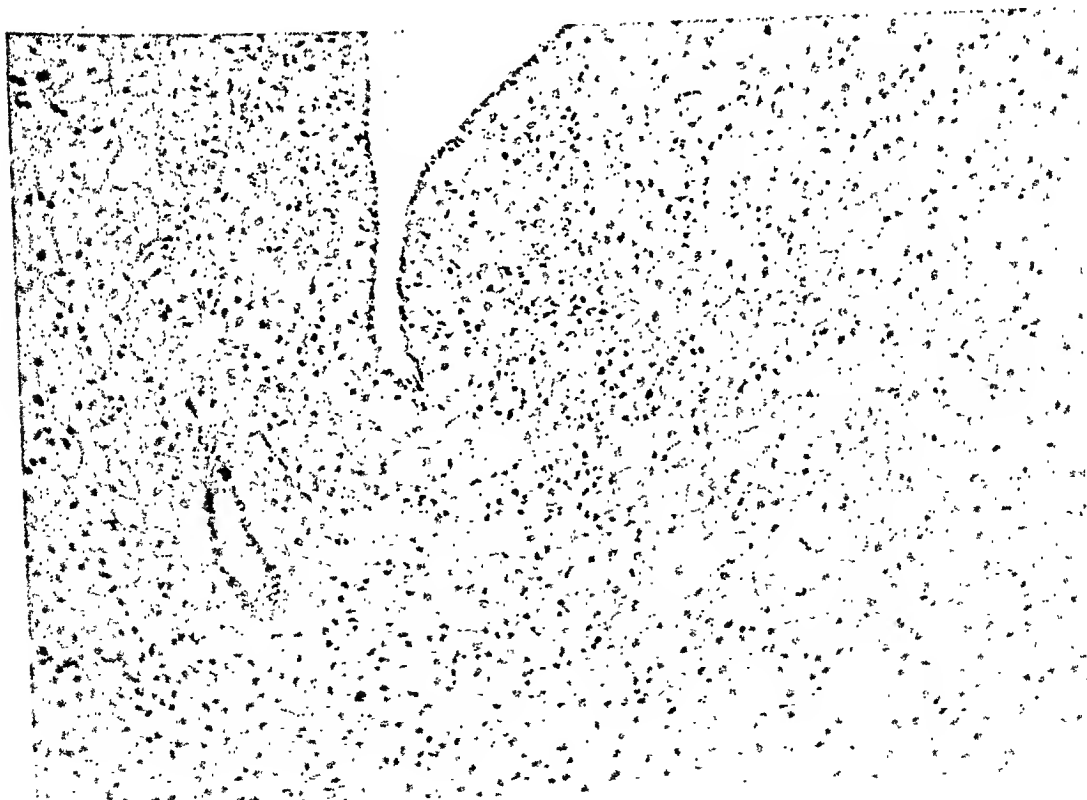


Fig. 6.

TABLE I

SPECI- MEN NO.	DATES	NO. OF DAYS	MOUSE UNITS ESTROGEN, PER 24 HR.	MG. ANDROSTER- ONE PER 24 HR.	MG. PREGNANE- DIOL	
1	9/26-20/42	3	89	22.5		Preoperative speci- mens
2	10/17-20/42	3		21.1		
3	10/20-23/42	3		21.0		
4	10/23-26/42	3	147	12.3		
	10/26-27/42	1			18.42 (calculated)	12/27/42 Ovariec- tomy
5	10/27-28/42	1		21.5		Postoperative speci- mens
6	10/28-29/42	1		16.8		
7	10/29-30/42	1		9.2		
8	10/30-31/42	1		11.2		
9	10/31-11/1/42	1		14.7		
10	11/1-2/42	1		9.9		
11	11/2-3/42	1		7.2		
12	11/3-4/42	3	15.2	7.8		
	11/5-7/42					
13	11/7-8/42	1		4.4		
14	11/8-9/42	1		8.5		
15	11/16-17/42	1		11.7		
16	11/17-18/42	1		11.3		
17	11/18-19/42	1			Too little to assay	

daily estrogenic excretion rate for menopausal women and women with amenorrhea due to cancer or tuberculosis varied from 0.37 to 0.57 estrone equivalent.⁶

The day before this patient was operated upon, a 24-hour urine sample was assayed for pregnanediol glucuronide by the method of Venning and Browne.⁷ These authors have studied the excretion rate of this substance in ten normal women for at least one complete cycle, finding the highest daily rate to be the equivalent of 8.1 mg. of pregnanediol.⁸ During pregnancy the rate rises as high as 100 mg. of pregnanediol per twenty-four hours in the last trimester.⁹ In the case we are reporting, 18.5 mg. of pregnanediol equivalent were found, very considerably more than occurs in normal urines at any time during the normal cycle. That this material was really sodium pregnanediol glucuronide in fairly pure form was shown by the melting point of 266° to 269° C. (melting point of pure sodium pregnanediol glucuronide = 268° to 271° C.).

Three weeks after removal of the ovarian tumor, a second 24-hour urine specimen was assayed for its content of pregnanediol. Not enough was present to permit assay. The inference is clear that the tumor had been acting as a functional corpus luteum producing progesterone, excreted in the urine as sodium pregnanediol glucuronide, and that with extirpation of the tumor this production and excretion were stopped.

Discussion

Is this type of tumor really adrenal in origin? Does it arise, as recent authors seem to think, from adrenal rests in the ovary? This is indeed a difficult question to answer, since the adrenal and the ovary arise from the same or very closely related embryonic cells situated along the genital ridge, and in many ways have similar or related functions. It is to be noted that when normal mouse ovaries are grafted into the ears of castrated males kept in cages at 20° to 21° C., they produce groups of cells which look very much like the cells of the adrenal cortex.^{10, 11} Aberrant rests of adrenal tissue are not infrequently observed in various parts of the body, especially along the course of the ovarian or spermatie vessels but, according to Novak,¹² such rests are rare in the ovary itself. Nelson,¹³ in reviewing the literature, finds accessory adrenals very common, but mentions only six cases in which adrenal cortex rests were found in

the ovary. He suggests that some of these may have been really masses of lutein cells. Kepler, Dockerty, and Priestley³ are the authorities for the statement that "it appears that adrenal rests within the ovary occur even less frequently than do these adrenal-like tumors."

In the present case, while the patient exhibited clear symptoms of masculinization, and a diabetic type of glucose tolerance curve, the histologic appearance of the tumor was definitely suggestive of an ovarian rather than an adrenal origin. In fact, the transitions occurring in this tumor from fibroblastic or mesenchymal-like cells, strongly suggesting its relationship to a theca-cell tumor, up to fat-laden cells presenting the rather typical appearance of adrenal cortex cells, may distinguish it as a sort of histologic connecting link between the theca-cell tumor and the so-called "adrenal cortical carcinoma of ovarian origin."

If these tumors really are tumors of accessory adrenal cortex, it is surprising that a higher surgical mortality does not attend their removal. In fifteen authentic cases there has been only one operative death,³ and this one from shock and hemorrhage rather than an adrenal reaction, whereas the danger of removal of adrenal cortical tumors is well recognized. Cahill's^{14, 15} figures are 39 per cent mortality (quoted from Cecil) or in the cases reported by him who showed endocrinologic stigmas, three deaths out of nine operative tumor removals.

That this tumor produced such a well-marked decidual reaction in the endometrium is another bit of evidence pointing to the fact that it was functioning as a corpus luteum. Novak¹² mentions another similar case and illustrates the outspoken decidualization of the endometrium brought about by the tumor, which he says must be interpreted as a luteoma. In contrast to this finding, Anderson, Hain, and Patterson¹⁶ have reported a case of a patient with true adrenal cortical carcinoma, during the examination of whom a curettage was performed. The endometrium is described as "scanty. Microscopically there are very few small glands in the resting phase."

When one attempts to determine the origin of such a tumor by measurement of hormones, one enters again on uncertain ground. If one says that such a tumor must be of adrenal origin because of the masculinizing symptoms: hirsutism, acne, voice changes, and large clitoris, it can be answered that the normal ovary has been shown to secrete male hormones. R. T. Hill¹⁰ has maintained the accessory sex glands in castrate mice by transplanting ovaries into their ears and keeping them at a low temperature (20° to 21° C.).

It is a well-attested fact that progesterone in large doses can be substituted successfully for adrenal cortical hormone. Progesterone prolongs the life of adrenalectomized animals,¹⁷⁻²⁰ mimics the action of desoxycorticosterone in causing water and salt retention,²¹ and, like cortical extracts, leads to cortical involution.²²

Animals adrenalectomized during pregnancy or pseudopregnancy survive longer than controls, presumably because of the action of their corpora lutea.²³⁻²⁵

Not only can the ovary take on some of the functions of the testis or the adrenal, but the reverse is also true, that the adrenal can replace the ovary. Woolley²⁶ removed the ovaries of female mice on the first postpartum day and observed that 100 per cent of the surviving animals showed evidence of estrogenic stimulation six months later in the size of the uterus, the state of the uterine glands, cornification of the vaginal mucous membrane, and the presence of irregular estrus cycles. Postmortem examination showed no remnants of the ovaries, but adenomas of the adrenals were present. Consequently, to argue about the nature of an ovarian or adrenal tumor on the basis of the presence or absence of certain hormones is not likely to be conclusive.

Adrenal cortical tumors usually put out large amounts of male hormone, though this is not invariably the case. They have also been noted to excrete pregnanediol in the urine (Venning, Weil, and Browne,²⁷ Salmon, Geist, and Salmon,²⁸ and Anderson, Hain, and Patterson¹⁶), but this does not necessarily come from an increased secretion of progesterone since Cuyler, Ashley, and Hamblen²⁹ have shown that desoxycorticosterone acetate also may be excreted in this form. It is tempting to suggest that the pregnanediol found in adrenal tumor cases is a metabolic product of adrenal 17-ketosteroids rather than progesterone, and that this explains the failure to find decidua in the case of Anderson, Hain, and Patterson.

We would interpret the high pregnanediol excretion rate coupled with a comparatively low 17-ketosteroid output and the decidualization of the endometrium in our case as a true progesterone effect.

It should be pointed out that they found 215 mg. of androsterone equivalent per 24-hour urine collection as compared with 22 mg. in our case. They found 8 to 15 mg. of pregnanediol a day; we, 18.5 mg. Perhaps when more is learned about the relation of hormones to tumors the ratios of one sort of hormone to another will prove of more significance in determining the origin or nature of a tumor than is now the case.

Summary

1. A patient suffering from a rare tumor of the ovary, variously named luteoma or adrenal cortical carcinoma of the ovary, or masculinovoblastoma, is described.

2. The tumor was successfully removed surgically, and proved microscopically to resemble a theca-cell tumor of the ovary in parts, the cells grading into others which resembled adrenal cortex.

3. The patient had marked decidualization of the endometrium, an observation thought to indicate the corpus luteum-like nature of the tumor.

4. The urine contained a moderate titer of estrogens, about double the normal female quantity of 17-ketosteroids, and a large amount of sodium pregnanediol glucuronidate. These findings are thought to show that the tumor was functioning more like a corpus luteum (high progesterone excretion) than like adrenal cortex.

5. We believe this tumor is best classified under the term "luteoma."

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LYMPHANGIOCYSTIC FIBROMA OF UTERUS

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I BELIEVE that there is no such entity as a fibroma of the body of the uterus, and only one cervical fibroma has been observed. Whatever is listed in medical writing under the headings of fibroma, or "fibroid," is actually a myoma uteri. There does, however, exist a rare uterine tumor of the connective tissue group, namely, the lymphangiocystic fibroma. It has been named and described by Robert Meyer; slides of most of the pertaining case reports have been seen by him. Rare as this tumor is, surgeons, gynecologists, and pathologists should be familiar with it in order to prevent an unwarranted diagnosis of sarcoma. I find that textbooks of pathology, gynecologic pathology, and gynecology do not deal with the subject. Cases have been reported by Robert Meyer (1924, 1930), Isbruch (1927), H. O. Neumann (1929), Carl Kaufmann (1931, 1932), Dworzak (1932), Motylofi (1932), Muschik (1933), M. Brenner (1934), Pahl (1934), and Limburg (1942). A tumor described under another name by Wolfgang Renter in 1915 belongs here, and, perhaps, a case registered as "fibroid with perithelioma and necrobiosis" by A. H. F. Barbour in 1913. There seems to be no other mention in English or American literature.

Case Report

The patient was a 50-year-old gravida iv. para iv, complaining of irregular periods for one year. During this time, the menstrual intervals had varied from three weeks to 3 to 4 months. For a few months prior to admission, the periods had been profuse and there had been intermenstrual spotting, weakness, and backache. The last period was three weeks before admission to Beth Israel Hospital. It was profuse, lasted ten days, and there was still spotting present at the time of admission. Past history irrelevant. Menstrual history: periods began at the age of 18 years, lasted six days, and occurred at 28-day intervals. Physical examination disclosed a well-developed, white woman, heart and lungs normal, abdomen soft, no masses felt, no pain elicited. Vaginal examination disclosed a parous introitus, slight rectocele, no cystocele, cervix 2.5 cm. from vaginal outlet. The cervix was hypertrophied. Protruding from the external os was a firm mass about 2 cm. in diameter. It had a pedicle which seemed to lead into the uterine cavity. The surface of this mass was smooth, covered by intact mucosa. The uterus was retroverted, about the size of a six weeks' gestation. The posterior wall of the uterus appeared irregular, hard, and nodular. The appendages were negative. The preoperative diagnosis was "submucous uterine myoma," partly situated in the vagina, and a small rectocele. Laboratory findings were within normal limits.

A vaginal hysterectomy and perineorrhaphy were performed by Dr. J. C. Porges under spinal anesthesia. The mass protruding from the external os was first cut off from its pedicle, which was found to be attached to the posterior cervical lip, only a short distance above the external os. The vaginal hysterectomy was then completed without difficulty. The patient made an uneventful recovery. The small tumor, on gross examination, was found to be round, ovoid, and partly cystic.*

*When seen, fifteen months after operation, patient was in good health, pelvis free.

The gross specimen was a uterus with cervix, total length 9 cm., the tubal angles were 4.8 cm. apart, the anteroposterior diameter was 5.5 centimeter. The cervical lips were everted, funnel-like. The uterine cavity was narrow. The endometrium was thick, partly yellowish, partly red. The myometrium was up to 2.5 cm. thick. No myomas were seen.

A pinkish gray, cystic, soft, ovoid specimen, largest diameter 3 cm., was received separately. It had an irregularly ovoid cavity. Its inside was glossy, purplish pink with irregular small, flat, ovoid protrusions. No attempt was made to find the site of attachment of this tumor, and no photograph of the gross specimen is available.

Microscopic Description.—The tumor was situated in the upper cervix. A layer of normal cervical stroma, 0.5 to 1 cm. thick, separated it from a zone of



Fig. 1.—General view of tumor. The adjoining cervical stroma is more deeply stained. The central cavity (corner) has no lining. There are several cleft-like cavities (azokarmin stain). (X56.)

Fig. 2.—Another portion of the tumor, empty cavities, clefts, no linings (azokarmin stain). (X56.)

severe cervicitis. Nowhere did the inflammation reach the tumor. The outer edge appeared sharp to the naked eye in the stained section. Microscopically, however, no capsule was found, not even a pseudocapsule; the adjoining tissue was not compressed. Finger-shaped portions of tumor and of normal tissue interlocked (Fig. 1). Even small portions of cervical stroma, which appeared entirely surrounded by tumor, looked normal. Slight loosening of texture was the only indication of histolysis.

The tumor was roughly ball-shaped. It represented a shell, 0.7 to 1.5 mm. thick, surrounding a ragged cavity, or rather a central cavity, which in turn was surrounded by a system of clefts. If the evidence of numerous single sections can be trusted, most of these clefts did not communicate with each other

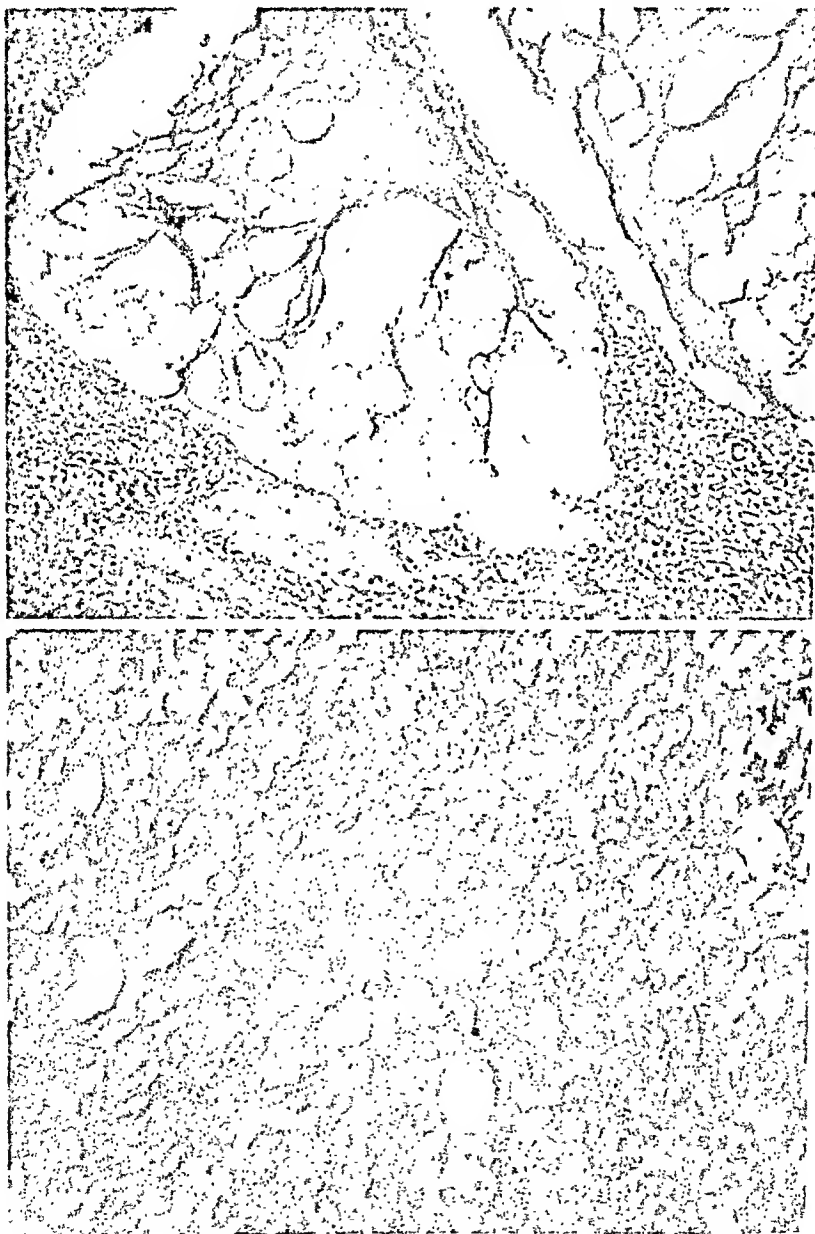


Fig. 3.—One of the larger cavities; it contains homogeneous matter (azo-karmin stain). ($\times 95$.)

Fig. 4.—Beginning liquefaction (center), with a few round swollen nuclei. A small blood vessel near the lower edge. At this magnification the structure of the tumor becomes recognizable (azo-karmin stain). ($\times 360$.)

(Fig. 2). Some were empty, others were filled with thin, homogeneous matter or with a "fuzzy" coagulum. In most places, no lining layer was seen, the tumor tissue ended abruptly. At some points, a single layer of flat cells with closely arranged oval nuclei lined the cavity. Occasionally, such a layer had been lifted off the underlying tissue, thus revealing its character as endothelium of a lymph vessel. Cross sections of blood capillaries protruded from the nonlined inner surfaces; obviously the vessels were more resistant than the tumor tissue proper (Fig. 6). Smaller, indistinctly outlined spaces in the tumor also were occupied by coagulated fluid. They were precursors of the larger cavities (Fig. 3). One of them was traversed by a blood capillary (Fig. 5). There was, however, no hemorrhage anywhere in the tumor. Small groups of red blood cells, or single ones, were found in the tumor. But, invariably, the wall of a

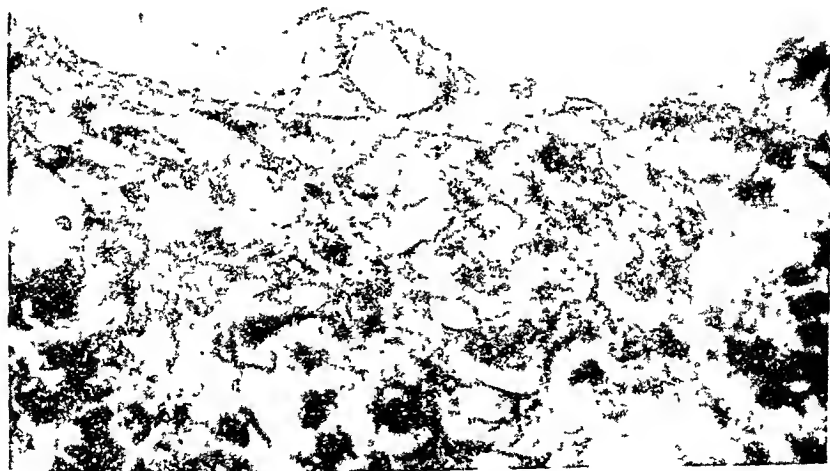
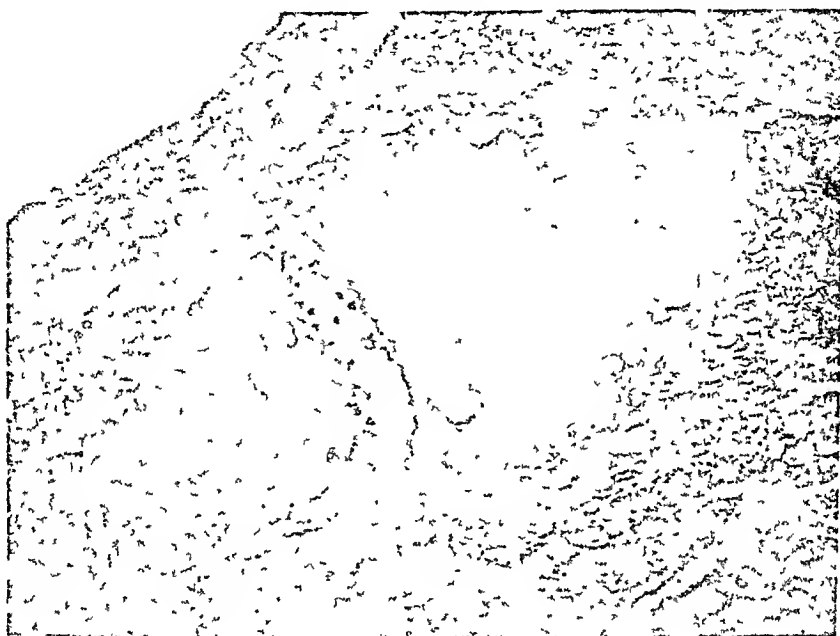


Fig. 5.—Advanced liquefaction. An intact capillary crosses the liquefied area (azokarmin stain). ($\times 220$.)

Fig. 6.—Edge of cavity, no lining. A blood vessel has withstood the liquefaction process and protrudes, knob-like, into the cavity, with remnants of tissue next to it. Note the structure of the tumor (azokarmin stain). ($\times 670$.)

capillary was found in the neighborhood, and the red cells might have been intravascular. Small areas of liquefaction were numerous, notably around blood vessels and lymph vessels. It stands to reason that numerous lymph vessels were incorporated into the cavities which resulted from liquefaction; direct proof of this is lacking.

Vessels were very numerous, most of them were sinusoidal capillaries or venules. Vessels with a distinct muscularis were few, and thick-walled ones were found at the periphery only. There were blood vessels, lymph vessels, and there were endothelium-lined spaces whose nature was doubtful. Some looked like lymph vessels, but they contained red blood cells.

An even network of collagenous bundles occupied the tumor. (Figs. 7 and 8.) They appeared red in the van Gieson stain, blue in the azokarmin, and

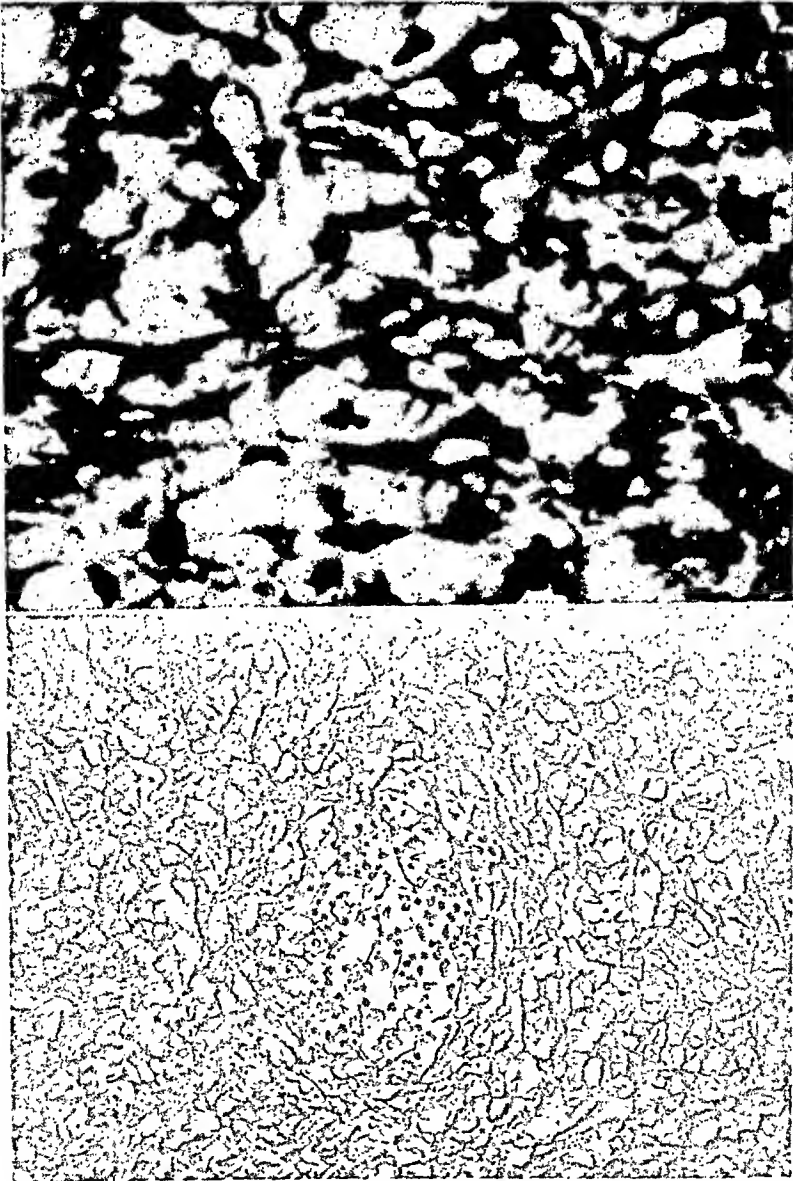


Fig. 7.—An inextricable network of cells, thick fibers and thin fibers (azokarmin stain). ($\times 960$.)

Fig. 8.—The fibers have been dissolved by the action of lymphocytes (center). At the edge of this area, the network is denser and somewhat reticulum-like (Bleischowsky-Maresch stain). ($\times 220$.)

dark brown in the Bielschowsky stain. At the outer edge, the fibers were continuous with those of the cervical tissue (Fig. 1). Parallel or radial arrangement was not conspicuous. Thin fibers seemed to merge with the cytoplasm of the tumor cells; their staining reaction varied (Fig. 7). Some very thin fibers sprang from thicker ones at a right angle, like the teeth of a comb, thus resembling "gitterfasern" in shape; but they all became light brown in the Bielschowsky stain. At the edge of an area (diameter 160 microns) which was occupied by small round cells, the fibers became almost black in the silver stain. Obviously a lymph node had been beginning to form in the tumor (Fig. 8). No elastic fibers were found, and no muscle fibers. The cells which formed the tumor were very evenly distributed; there were neither heaps, nor bundles, nor whorls. The picture was the same from the periphery to the surface of the central cavity. No cell boundaries could be recognized. One gained the impression—in the paraffin section from material fixed in formalin—that many tumor cells were star-shaped and touched each other (Fig. 7). The nuclei were more or less oval, on the average 6 to 9 microns long. The distance between nuclei averaged 8 to 10 microns. The chromatin particles were small, there was condensation near the membrane in some nuclei. A single medium-sized nucleolus was seen in many cells. Occasionally, 3 to 5 nuclei were close together, but there were no giant cells (Fig. 9). No cell division was found.

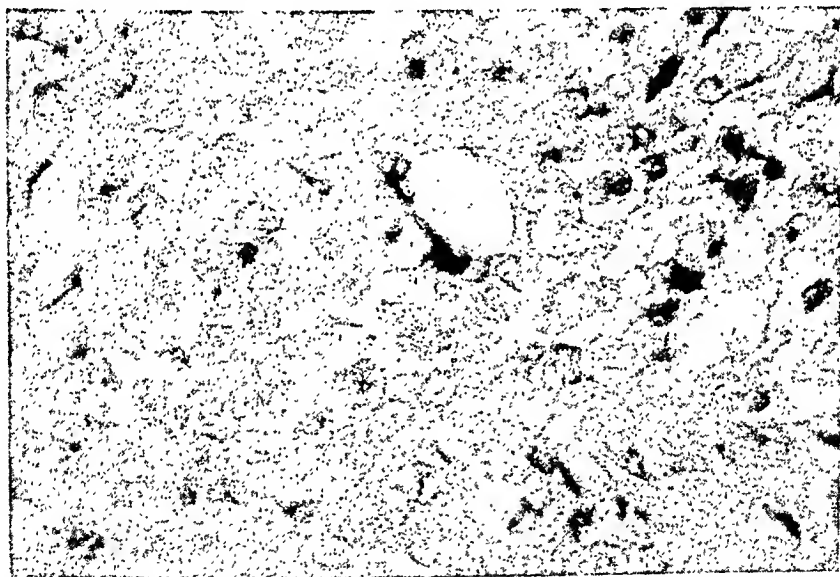


Fig. 9.—In one half of the picture, the nuclei are large and clear; occasional single nucleoli are visible. Smaller denser nuclei predominate in one corner. No outlines of cells can be seen (hematoxylin-eosin stain). ($\times 670$.)

Single small compact round nuclei were sparsely scattered; they probably were lymphocytic. Two loose heaps of such cells were detected on continued search. In the above-mentioned areas of liquefaction, slightly larger, dark nuclei were found in groups; and around some, a narrow zone of cytoplasm could be recognized. They may have been degenerating tumor cells (Fig. 4). One single cell, surrounded by ordinary looking tumor cells, had small indistinctly eosinophilic granules. Tissue mast cells were numerous, one to three in the high power field; they were irregularly distributed, not related to blood vessels. Occasionally three or five of them were close together. The uninfamed cervical stroma which surrounds the tumor contained only few mast cells.

Anatomic diagnosis—Hyperplasia of myometrium, small lymphangiocystic fibroma, cervicitis.

Comment

This case is the twentieth (or twenty-first) reported. A satisfactory tabulation of the cases as to age, parity, size of tumor, occurrence of hemorrhage, etc., must await larger series of complete observations in surgical pathology and in the autopsy room. While the same might be said about the anatomic features, the picture, gross and microscopic, seems sufficiently well established to distinguish the lymphangiocystic fibroma from other uterine tumors.

Of twenty patients,* two were under 30 years of age, none under 28 years, eleven between 40 and 50 years, three between 50 and 60 years, and one over 60 years. These figures represent the ages at the time the tumor was discovered. The available data reveal nothing about the age at which the tumors began to develop. Small size, in this tumor as in others, may indicate an early lesion, but not necessarily so. C. Kaufmann's third specimen was not larger than a hazel nut, and the absence of large lymph cysts was interpreted as evidence of an early phase. This is probably correct. But the tumor described in this paper is hardly larger and contains, nevertheless, a relatively large central cavity. The lymphangiocystic fibroma probably belongs to the period of declining sex-life. The age of the patient and the size of the tumor reveal no consistent ratio. The figures on parity and on the time elapsed since the last pregnancy are not significant. Coexistent myomas are not more frequent than expected. Adenomyosis is mentioned in one case. There is no preferred site. One tumor was intraligamentous, one (here described) was cervical, the others occupied any portion of the corpus. The central cavity in some was filled with blood; in others, the fluid was light greenish; the data on this point, as on others, are incomplete. Four of the tumors were very large (man's head, child's head, 24 by 16 by 14 cm.). Most of them were between the sizes of a hen's egg and an orange; a few were less than 4 cm. in diameter. The amount of tumor tissue is much smaller than these figures seem to indicate, because most of the volume is occupied by cavities. In two head-sized tumors, the shell of tissue did not exceed 1 cm. in thickness. In smaller tumors, the tissue layer generally was relatively thicker. There is nothing characteristic about the clinical symptoms and, notably in the case of small tumors, it is quite doubtful whether the gynecologic symptoms noted are at all connected with the tumor.

The distinguishing gross feature is a central cavity with variously shaped, mostly flat, ovoid, large, or small protrusions. This picture is unlike that resulting from excessive edema in the so-called "cystic myoma." A cavity without endothelial lining may nevertheless represent a true lymph cyst in which the endothelium has been destroyed; it may as well be the result of accumulation of fluid in preformed tissue spaces; and it can finally be a combination of both. The cystadenofibromyoma described by Hans Limburg (*Ztschr. f. Geburtsh. u. Gynäk.* 115: 17, 1937) presented a somewhat similar gross picture. In very large tumors, notably in the presence of hemorrhage, the central cavity might not be distinct, and, in very small tumors, no large cavity may be present. But the typical lymphangiocystic fibroma is never entirely solid. The tumors fre-

*In an additional case the age is not given.

quently protrude into the uterine cavity or narrow it when they are large. In the case described here, the tumor seems to have been pedunculated; this has not been observed before, it may be connected with the, equally unique, location in the cervix. The outline of the lymphangiocystic fibroma appears sharp to the naked eye.

Histologically the tumors differ from other uterine tumors by their cellular and fibrillary fibromatous structures, and from any variety of myoma by the absence of muscle fibers. The next characteristic feature consists in the numerous lymph vessels. All other histologic details are less constant. Large, partly thick-walled, blood vessels are conspicuous in many tumors. In four cases giant cells have been described. Elastic fibers, except for the blood vessels, are absent. In the tumor described here mast cells are numerous; they are another expression of the connective tissue character of the lymphangiocystic fibroma.

It hardly needs to be mentioned that we are ignorant about the origin of lymphangiocystic fibroma. Robert Meyer puts it into the group of hamartoblastomas, i.e., tumorlike structures resulting from a flaw in development.

The question of possible malignancy is of greater interest to the physician. The cellular pattern is never quite regular, often rather irregular, "sarcomatoid." The tumors have no capsule and, microscopically, no distinct outline. But thus far it seems that the lesion is essentially benign. Considering the small number of reports available, we cannot yet be as confident in the good prognosis as we are with the Brenner tumor. The war has made follow-up in Europe impossible, and so far all cases reported have been observed in Europe. The fate of Motyloff's patient (*Case 1*) must make us cautious. This case was originally described as lymphangiocystic fibroma from Robert Meyer's laboratory. It concerned a 56-year-old para iv, whose previous history was irrelevant. She had entered the menopause at the age of 48 years. Four months before operation she noticed abdominal pain. A fist-sized tumor was palpated in her abdomen; it was interpreted as ovarian cyst. At operation a tumor, 7 cm. largest diameter, was found on top of the uterus; it was firmly adherent to the vermiform appendix. In the histologic picture giant cells, which, as mentioned have been found in a few other cases, were very conspicuous. In concluding, Motyloff wrote that so far (1932) neither recurrences nor metastases had been observed in lymphangiocystic fibroma, but that the number of published cases was too small. While Motyloff's paper was in print, the patient developed a recurrence and died. The recurrent abdominal tumor was a spindle-cell sarcoma without giant cells. Thereupon, Robert Meyer had the case restudied by Johannes Pahl. A detailed description of the peculiarities of this case was given, and the conclusion was reached that this tumor should not be called lymphangiocystic fibroma. It was considered as related to it but not identical. It was called a hamartoma (*Fehlanlage*) of the connective tissue with sarcomatous degeneration.

Such a tumor, or a similar one, might lead to a grave mistake in differential diagnosis, and to uncertainty concerning operative procedure. No pathologist could dare to make a definite diagnosis from a rapid frozen section when confronted with a specimen as in Motyloff's *Case 1*. Perhaps the presence or

absence of adhesions will be a guiding factor, as it is in the ovarian dysgerminoma. A small lymphangiocystic fibroma situated within an otherwise not remarkable uterus, however, can be considered a harmless lesion. It does not appear justified to treat a young woman "as if she had had a sarcoma of the uterus" (Dworzak) because structures similar to those of sarcoma have been found in a perhaps small lymphangiocystic fibroma. The question of differential diagnosis is closely linked to that of prognosis. In most instances it will offer no difficulties; the microscopic picture is highly characteristic. Secondary changes in an angiofibroma of the uterus might perhaps result in a picture resembling lymphangiocystic fibroma, but these tumors are extremely rare. It remains to be seen whether or not sarcomatous uterine tumors will be encountered again which resemble the benign lymphangiocystic fibroma. If such cases differ from the ordinary lymphangiocystic fibroma in the gross by the absence of cysts, this peculiarity may be helpful in operating room diagnosis.

The problem of prognosis has been further complicated recently by Linburg's case in which a lymphangiocystic fibroma was combined with malignant endothelioma.

The patient was a 35-year-old primipara. Eight years before, two years after delivery, she had been everted. Laparotomy was performed for myomata uteri, but, when the surgeon saw the uterus, he diagnosed pregnancy in the fourth month and closed the abdomen without removing anything. A few months later the patient had severe bleeding; the uterus gave a large shadow on x-ray but no skeleton could be seen; the breasts contained colostrum. A supravaginal hysterectomy was performed. The uterus weighed 11.5 lbs.; a mass 20 by 18 by 9 cm. occupied the fundus and the posterior wall, it contained 4.5 liters of clear amber fluid. The serosa was smooth. The tumor consisted of a large thin-walled (2 to 5 mm.) cyst into which a partly whitish and firm, partly yellowish and soft solid mass, 13 by 12 by 6 cm. protruded. The endometrium and the appendages were not remarkable. Microscopically the picture was that of lymphangiocystic fibroma, but in addition there were thick endotheliomatous structures which lined the large cavity without invading the underlying tumor. Eighteen months after operation the patient died in caehexia with huge tumors throughout the peritoneal cavity, and with a tumor in the supraclavicular and bronchial lymph nodes. The metastases consisted entirely of endotheliomatous masses; they contained no structures resembling the lymphangiocystic fibroma.

This tumor, which is unique, must caution us in making a prognosis, not in the typical cases of lymphangiocystic fibroma, but in any such tumor that differs from the usual type and that has additional tissue elements whose clinical dignity is not fully understood.

The lymphangiocystic fibroma has not been found in autopsy material so far. This may be attributed to lack of attention, or these tumors perhaps undergo changes with the aging of the bearer. In this connection an observation made by Askanazy may be helpful.

During the autopsy of a 71-year-old woman, a chestnut-sized, sessile, well-circumscribed tumor was found under the endometrium. It was not as firm as a fibromyoma, its cut surfaces were porous and granular. Microscopically, no muscle fibers were found. The tissue consisted of collagenous bundles, between

which a very loose tissue was situated; this was split into fine fibrils by the lymph stream, and it was permeated by clefts which had no cellular lining. There were some blood vessels, very few lymphoid cells, and occasional small groups of small spindle cells. The tumor was well-demarcated from the surrounding myometrium.

As Askanazy writes, "Such a uterine fibroma which has nothing to do with a sclerosing myoma . . . may be compared to the fibroma lymphangiocysticum. . . . There are no lymph cysts but the flooding of the tissue spaces by lymph is striking." This structure (no picture is given) may perhaps represent a late phase of lymphangiocystic fibroma.

It is hard to believe that a tumor of such unusual gross and microscopic aspect should not have caught the eye of earlier observers. But, in going through Kelly and Cullen's monograph on myomas of the uterus, one finds no indication that the authors may have encountered a lymphangiocystic fibroma. It is the same with the thirty-one cases of what was called "perithelioma and endothelioma" of the uterus collected by Dorland in 1916. A number of case reports bearing suggestive titles (angioplastic sarcoma, angioplastic mesenchymoma, endothelioma, lymphatic reticulo-endothelioma, angiofibroma) were investigated with the same negative result.

Robert Meyer, having seen ten cases in the course of eight years, stated in 1932 that the tumor cannot be so very rare. It remains to be seen whether or not reports on lymphangiocystic fibroma will appear in numbers during the coming years as those of the Brenner tumor did after 1932.

Summary

1. A case of lymphangiocystic fibroma of the uterus is described. It is the twenty-first one reported.
2. It appears that the typical lymphangiocystic fibroma is benign; sufficient follow-up data, however, are lacking.
3. Questions of diagnosis and procedure are discussed.

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EXPERIENCES WITH THE LABOR PROCEDURE OF GRANTLY DICK READ*

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THIS is a report of 168 cases delivered by the method of Grantly Dick Read¹ of London. These cases are unselected, except that they are 168 consecutive vaginal deliveries. They were delivered in a small general hospital, which has eleven beds for the maternity section. The series starts from the time the method became available until it was closed in preparation for this report. These women were delivered by me personally, chiefly in the year 1944, without the assistance of a resident.

Method

Grantly Dick Read published his method in the early 1930's. In the book *The Evolution of Obstetric Analgesia*² by Andrew M. Claye of Leeds, published in 1939, about a page and a half is devoted to this method, and the following conclusions are reached.

1. "Read has performed a great service to obstetrics."
2. "With much of what Read writes, I am in agreement, but I question whether the whole procedure is feasible for the average mother."

It should be understood in the beginning that we are talking about the normal case only. The psychological processes of the female in preparation for mating, for impregnation, for pregnancy, for parturition, for the care of the young, for their rearing, and for the family after the young have grown are the most powerful emotional processes known.³ This is universally recognized by everyone from the backwoods farmer to the most learned psychiatrist. As it concerns woman, a whole system of psychiatry is built upon it.

From the time she is able to toddle, the little girl identifies herself with motherhood by playing with dolls. As she grows older into the time of puberty she dreams of impregnation and the production of children. When she is grown and married, she desperately wishes to have babies. One might say that these feelings, emotions, wishes, and drives are literally what makes the world go round. When a woman presents herself in the waiting room of an obstetrician as a prenatal case, one is apt to see a very sedate young lady who is outwardly calm and serene, but if one should take the trouble to inquire, or study and find out, he would discover that he is face to face with a psychological force almost unbelievable.

This theory is a deliberate attempt to harness, direct, and control these feelings in a woman, so that when the time comes for her to go into labor, they

*Presented at a meeting of the Philadelphia Obstetrical Society, Oct. 4, 1945.

are turned into beneficial channels, and the woman is thus aided to have her baby.

When she goes into labor, one must remember that her whole life up to this time has been in preparation for this event. It has been thought about, longed for, prepared for. It is the fulfillment and culmination of all that the girl intended to do and become. Nothing could have turned her aside from it, or stopped it.

Helene Deutsch⁴ says that obstetrics is a man-made science and is "a masterpiece of masculine efficiency, but deprives woman of her active participation in delivery, and this in a certain sense deprives her of her monopoly in this field."

As I have seen it practiced up to now, the safety of the woman and her child have been paramount, and they should still be paramount; but little attention has been paid to her ideas and wishes on the subject. If she is handled in an unsympathetic way, or allowed to become frightened, all the power and the built-up emotions that have gone before are turned into an agony of anxiety, fright, and apprehension, and we have on our hands a woman who is complaining bitterly of pain and, at the end, screaming with agony and fright, the fear of death, the fear of dismemberment, and almost any fear that can creep in at such a time.

A typical example of the way we have been handling our maternity cases is as follows:

The woman has been coming to the doctor's office once or twice a month. She has been examined. She has been told what to eat, what to do to keep herself healthy. She has been x-rayed and tested, and everything is found to be normal. In the middle of the night, she goes into labor. She rouses her husband and says, "I'm in labor. Call the doctor!" If it is a young husband, he is apt to respond, "I hate to call the doctor at this time of night. Can't you wait until morning?" She becomes impatient at this obstruction placed in her way and commands, "You call him now!" The doctor is aroused by the telephone at 3 A.M., and the husband says apologetically, "Doc, I think my wife is going into labor." The doctor is apt to think, "Oh, my, I hope she will wait until morning," but he says to the husband, "When her pains are coming every ten minutes take her to the hospital." So the prospective parents wait in a nervous tension for the pains to start to come as often as ten minutes apart. When this happens, they proceed to the hospital. The community is dark and they have a feeling of great loneliness. They arrive at the hospital and the corridors are dark. The nurses are quietly appearing and vanishing. One of the nurses takes the patient, asks a few impersonal questions and sends the husband off to wait. The woman is taken, prepared, put in a labor room, and may be seen by a resident, if the hospital has one. And so she gets on with her labor. The pains get harder and harder until morning when she rings for the nurse and inquires, "Where is my doctor?" The nurse answers, "He will be here in plenty of time." About 9 A.M. the doctor turns up, examines the woman, and reassures her by telling her that everything is all right. The woman asks in a weak voice, "How long will it be?" The doctor replies, "I don't know. It won't be too long." He administers a sedative, and off he goes because he has a million things to do. After this the pains get worse and the woman rings for the nurse again and queries, "Where is my doctor?" The nurse murmurs, "He has a lot of things to do and he will be here in time—

now just get on with this." When the pains are really getting to be agonizing the woman is turned from a serene, sedate person into an hysterical, moaning, or screaming individual who has lost all control of herself.

I am ashamed to say that I myself have conducted many labors in this fashion and took it for granted that labor was supposed to be this way. I have seen many statements in the textbooks that there is no necessity for the doctor to get up at night at the beginning of a labor case, particularly if the woman is a primipara, provided she is under the care of a good nurse.

Under the system as promulgated by Read, the basis of the theory is that the pains of labor are caused by fear. The cervix relaxes owing to impulses originating in the autonomic system. This system stimulates the cervix to relax and to allow itself to be transformed into the lower uterine segment, but the sympathetic nervous system also has a connection to the cervix. The upper end of the sympathetic is connected with the thalamus, the seat of many of the primitive emotions, especially fright and fear. At the beginning of labor, the cervix is pulled on by the muscle contractions from the fundus. The thalamus becomes aware of this through its connections with the sympathetic and autonomic systems, and an awareness of a new sensation is aroused. The thalamus, through the cortico thalamic connections, informs the gray matter, usually by means of a misinterpreted impulse, that the woman is in pain. A reflex is set up through the sympathetic which overrides the relaxing efforts of the autonomic, and causes not only an absence of relaxation, but actually causes a spasm of the cervix.

In order to have more details of these nervous connections one would have to consult the work of Cleland⁶ and others, but it is simply understood if we reason by analogy, that the uterus is a hollow muscular organ like the bladder, the rectum, or the gall bladder, and that it is provided with a sphincter or detrusor muscle. With hollow organs other than the uterus, when the organ contracts, the detrusor relaxes and thus the organ is evacuated. If anything interferes with the mechanism, such as a fissure in ano, a urethritis, or a stone in the common duct, spasm of the sphincter results, and tremendous pain is produced.

The more frightened the woman is, the greater is the tension on all her muscles and nerves, and the more severe is the spasm in the cervix, and the harder is the pull to open it. As I understand it, a spasm or cramp is created with the cervix pulling in one direction in its effort to stay closed, and the fundus making strong efforts to open it. Real pain is thus produced, and it becomes increasingly great as labor proceeds.

If the woman is taught to have no fear, and to understand the processes of labor, and if she is taught to relax all of her skeletal muscles, and if she has seen her physician in the beginning of labor, and if the nurses who are attending her understand this process, the cervix will relax also, and will allow itself to be transformed along with the isthmus into what we know as the lower uterine segment. This can and should occur without pain. Labor progresses in this way until the end of the first stage. At the end of the first stage, the head is forced through the cervix, and this causes some pain. The woman is taught that, when she can no longer relax, the head is very apt to be coming through the cervix, or conversely, the cervix is being pulled over the head. She is taught to wait for this moment and to expect it. At the end of this time, the longitudinal muscles of the uterus as well as the muscles of the abdominal wall come into play. The sensations of the woman change entirely, and she is relieved of the pain which was caused by the distention of the cervix, by bearing down.

During the prenatal conferences, she has been taught how to do this and works very hard, in the case of a primipara, for about an hour, and in the case of a multipara for one or two pains until the head is distending the perineum. She has been told what sensations she will have when the head is on the perineum. She expects the pressure and knows that the head will turn away from this structure at the last moment. She is supposed to do her work with the muscles of respiration and the abdominal muscles, as far as possible, and to relax the perineum so that the head can be maneuvered over it. If the woman has been a receptive subject, and most of them are, and her instructions have been thorough, and she has had good care during her labor, this whole process of labor is completed more rapidly than usual, and with comparatively little discomfort. She has been told that she may have an anesthetic at the end of the second stage, and when this stage arrives, it is offered to her. If an episiotomy is deemed necessary, the perineum is infiltrated with novocain, and the episiotomy is done.

This is a bare and brief outline. One can see that the technique of such a delivery is applied at the very first prenatal visit. The woman is examined thoroughly and any physical abnormality is corrected, if possible. If she is in poor physical condition, or suffering from anemia, calcium deficiency, or vitamin deficiency, these things are corrected. A genuine interest in her physical well-being and her mental state of affairs is shown by the doctor the first time she comes in, and at each subsequent visit. She is taught how to relax, and she is instructed to practice relaxation every day. Many women will neglect this. If the husband comes in with her (and this is encouraged) he listens to the doctor's explanation of the theory of labor and he usually will assist greatly by insisting that the woman carry out relaxing exercises. The patient is shown exactly what happens in labor by means of diagrams and pictures taken from Williams's textbook. I should say at this point, that pictures of the end of the second stage are not shown, but diagrams of how the cervix dilates, and pictures of the formation of the lower uterine segment are extremely valuable in helping patients to understand.

During these visits, the doctor stresses the importance of the baby. A great deal of discussion about the baby is encouraged—speculation as to its sex, whom it will resemble, how dearly the patient will love it, what fun she will have in taking care of it—all this is done for the purpose of focusing her mind on the child and away from herself. She is told that at the end of the second stage, the most exquisite sensation that she can ever have is to hear the first cry of her baby, and she is so eager listening for it and awaiting it that she forgets to be frightened and tense.

The upshot of all this is, that the process of labor becomes in her mind a great event and memorable occasion. It is the time when her baby is given to her, to hear, to see, to fondle, and to care for. What pain there has been, is lost in a kind of ecstasy and pride that comes over the mother during the labor, and at the actual delivery. Many of these women, whose records are being discussed, speak of their labor as one of the happiest and most pleasant moments of their entire lives.

Material

Number of women delivered	168	
Primiparas	62	
Multiparas	106	
Maternal deaths	0	
Fetal deaths	1	
(Premature baby died twelve hours after delivery)		
Postpartum hemorrhages	1	
(Readily controlled by the usual method)		
Forceps cases as follows:	9	
For occipitoposterior position	2	(Both multiparas)
For deep transverse arrest	2	(Both primiparas)
Big fetal head, low forceps	5	
Breech	2	(Both primiparas)
Twins	1	set
Face presentation	1	
All mothers well and out of hospital in ten days.		

Results

The two multiparas that had occipitoposterior positions, and the one multipara that had a face presentation, suffered intensely, and were not helped at all by relaxation. The two primiparas that had a deep transverse arrest, had slow labors and were given demerol. This usually required one or two injections of 50 to 100 mg. demerol each. These two women were helped by the relaxation according to their testimony. The second stage was carried out with rotation and delivery by forceps under anesthesia.

Of the rest, twelve multiparas stated that their labors were as painful, or more painful, than previous ones, and one multipara with four children refused to be bothered with it. The remaining ninety multiparas stated that they were helped greatly.

The term "helped greatly" should be explained. These women stated that they had no pain at all during the first stage, and mild discomfort at the very end of the first stage, that is, in the transition period between the time when they were able to relax, and when they felt impelled to bear down. The second stage in all cases consisted of about two to five expulsive efforts. All of the patients were offered ether as an anesthetic, but only four or five accepted it. In none of these cases was there any hysteria or uncontrollable crying and screaming. These women stated that they did not find the pain greater than they were willing to bear, and they felt that they needed no other pain relief. They stated that their labor had not been a dreadful affair, and if they had to go through it again they would not mind it under the same conditions. This was the statement of the most pessimistic. Most of the women said that the method was marvelous. They had actual discomfort only at the end of the second stage and stated that the pain was not really a pain but only a discomfort. They were surprised at the ease and smoothness of their delivery. In their language, "It did not amount to anything."

Of the 62 primiparas, two had deep transverse arrest. They had long and painful labors and required rotation in the second stage. Five others had very large fetal heads and required low forceps. Two cases were breeches. Both of these patients were nurses, and their deliveries were without incident. One stated that she had no pain during her delivery. Both women knew beforehand what the position of the child was, both had gynecoid pelvices by Caldwell's classification, and normal measurements. The first stages were without discomfort. The second stages were managed without interference except for a deep episiotomy, up to the delivery of the head. It had been explained to the women how important it was to push the baby out and not force the attendant to pull upon it. When the time came for the head delivery, Mauriceau's maneuver was tried gently in both cases, but the heads did not deliver, so forceps were applied and the heads were lifted out.

This leaves 53 cases remaining, and the method seemed to succeed in forty-eight. The other five were frightened, groaning, and complaining women all through their delivery. Of the 48 successful cases, very little pain was experienced. Ten of these primiparas could not relax because the pain was a little too severe in the first stage. In such cases demerol was given in small amounts of 50 to 100 mg. Usually one injection was required, and never more than two. As they said, this injection "took the edge off the pain" and they were then able to relax until the second stage began. The second stage lasted usually about an hour, and required from twelve to forty expulsive efforts. In all primiparas the perineum was infiltrated with novocain, and a small episiotomy done.

The conduct of the patients in whom this method succeeded was striking. There was a great calmness and cheerfulness. There was no crying, screaming, or groaning, although there was usually considerable grunting during the bearing-down period. These women stated that they enjoyed their labor because it was such a great event and because the pains were not bothersome.

One learns early, when applying this system, to listen carefully if a patient complains of pain such as one sees in ordinary delivery. Such a complaint calls for an immediate and careful examination with another x-ray study if necessary, because many times occipitoposterior rotation will be found. This calls for a change of plan. If the occipito is found by examination to be anterior and the patient is complaining, then the head is very large or the patient is unduly tense. The obstetrician will have to judge for himself which is the case. It is not always possible to banish enough of the fear to obtain self-control and relaxation, as in the case of a young primipara whose mother and grandmother came to my office and recommended a section because, as they stated, "She is the biggest baby in the world and never had one iota of self-control." Vaginal delivery was elected, and when labor started they brought the patient to the hospital and said to me, "Well, here she is. God help you." Then they went home and took the telephone receiver off the hook. They might well have closed the windows too, because the whole town heard every pain. After some hours a normal delivery was finished, and the patient asked for scrambled eggs and coffee.

Summary

It would seem that the method of Grantly Dick Read, when carefully applied, is valuable in relieving the pain of normal childbirth in about nine out of ten women. The pain is relieved to a greater or less degree. Some women had no pain to speak of, to use their language, in the first stage, while others could not relax until demerol was administered, after which the method succeeded. The effects during the second stage were very apparent, but the end of this stage required other help in some cases, that is, either ether anesthetic or novocain locally, or both.

Conclusion

The method of Grantly Dick Read is a valuable contribution to obstetrics. It is easy to apply and should have wide application. More research should be done so that its degree of perfection will be greater. No harmful results were noticed from its use. It has one drawback. It is very time consuming. Read contends that the normal woman in normal labor should have no more pain than she is willing to bear, not able to bear, but willing to bear. Any pain in excess of this, as well as hysteria and other forms of loss of nerve control, are caused by fear. The study of these women and their labors seems to substantiate his views.

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THE INDUCTION OF LABOR WITH METHERGINE*†

Preliminary Report

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METHODS for the induction of labor have changed little in the past decade. In vogue at one time or another was the use of castor oil, quinine, hormones, pituitary extract, alone or in combination with rupture of the membranes, tamponade of the lower uterine segment and vagina, insertion of a hydrostatic bag, and insertion of a bougie.

Because the drugs in use at present for the induction of labor are not ideal, we have initiated the study of a new synthetic ergot preparation designated as "methergine."

Pharmacology

Methergine was first obtained by Stoll and Hofmann.¹ Ergonovine on hydrolysis yields hydroxyisopropylamine and lysergie acid. Methergine is obtained by condensing isolysergie acid azide with d 2 amino 1 butanol and subjecting the product thus formed to a transposition treatment. The apparent similarity of methergine to ergonovine is seen by comparing their structural formulas. As shown by Stoll,² methergine contains one more CH_2 group than ergonovine.

Kirchhof³⁻⁵ et al., report that methergine is the only synthetic lysergie acid derivative which has any marked uterine motor action. These same workers report that methergine and ergonovine have comparable effects on isolated muscle strips from guinea pig and rabbit uteri. They have shown that in responsive uteri both drugs elicited a motor action that came on promptly and a similar, nearly identical, type of contraction.

Comparison of the use of ergonovine and methergine shows definite advantages in the use of the latter product. Adair,⁶ and Davis,⁷ report that in human subjects, ergonovine does not affect pulse, blood pressure, or urinary output. This was also found to be the case with methergine. However, Smith⁸ reports that ergonovine causes a slight increase in systolic and diastolic blood pressure with slight slowing of the pulse and Goodman and Gilman⁹ state that ergonovine causes little or no rise in blood pressure when injected intravenously in anesthetized cats and dogs. In contrast Kirchhof and his associates³⁻⁵ report that methergine was found to have an adrenergic action on the blood pressure of anesthetized dogs and to stimulate respiration in rabbits. These same workers have also shown that methergine lacks a sympathicolytic action. It failed to decrease the epinephrine rise on the blood pressure of the dog or to inhibit the epinephrine motor response of the isolated rabbit uterus.

Davis, Adair, and Pearl⁷ report that ergonovine is the only alkaloid of ergot which is effective by oral administration in small doses. When administered in doses of from 0.2 to 0.4 mg. by mouth it causes a typical ergot response, and uterine motility is established which becomes more vigorous in character as the uterine tone is diminished. Kirchhof,⁴ was able to show by a

*Read, by invitation, at a meeting of the Philadelphia Obstetrical Society, Oct. 4, 1945.

†Methergine (Sandoz) used in this clinical study was supplied by Sandoz Chemical Works, New York City, through the courtesy of Mr. S. M. Fessel.

locographie record that methergine solution containing 0.2 mg. per c.c. when given orally in three minim doses was able to increase uterine tone and motility in a patient at term but not in labor.

Moir,¹⁰ reports that before the onset of labor the uterus is apparently somewhat insensitive to the action of ergonovine. Adair⁶ and his co-workers report that ergonovine gave inconclusive results when it was tried in a few cases for the induction of labor, and Smith⁸ reports the same when it was used for the interruption of a five months' pregnancy. This is in contrast to methergine which has a pronounced effect upon the uterus before the onset of labor.

Smith⁸ states that nausea and vomiting have been encountered following the administration of ergonovine orally. This was not found to be the case with methergine.

Method

The preparation used contained 0.25 mg. methergine per c.c. All doses were given orally, diluted with approximately 10 to 15 c.c. of water. Every dose was given personally by the author, and each case was personally supervised throughout the entire induction.

In the first 11 cases only five minims of methergine were given every hour for five doses. It was then felt safe to increase the dose to $\frac{1}{2}$ c.c. for the first dose and 1 c.c. every thirty minutes thereafter for four doses. There have been no adverse effects with the larger doses employed, and the effect on the uterus is more pronounced.

Both the blood pressure and fetal heart were checked and recorded before each dose was given. The uterus was palpated following each dose to determine if any tetanic contractions occurred.

Indications

The indications for the induction of labor are principally maternal, but may be fetal or both. The principal maternal indications are toxemia of pregnancy, pernicious vomiting, intrauterine fetal death, and premature rupture of the membranes. The fetal indications are postmaturity and polyhydramnios. Under maternal and fetal indications can be listed premature separation of the placenta and placenta previa.

Among the contraindications may be listed any acute infectious disease such as pneumonia, influenza, or meningitis. The presence of any one of these diseases makes delivery an added burden. Titus¹¹ points out that patients with severe cardiac disease who have suffered decompensation should not be induced until compensation has been restored. Cephalopelvic disproportion is an absolute contraindication for the induction of labor.

Results

The results are divided into two sets of tables in order to evaluate the two different dosage schedules used. To determine whether or not the drug was successful in the induction of labor, the following arbitrary criterion was established. If regular labor pains began within six hours following the last dose of methergine, the induction was considered successful. Six hours was decided upon because it was thought that the effects of methergine would have disappeared by the end of that time.

One case of missed abortion is included here. This patient was a 32-year-old para ii who was six months pregnant according to her last period. She was bleeding slightly on admission. Vaginal examination revealed a uterus which

TABLE I. RESULTS OBTAINED WITH FIVE MINIM DOSES OF METHERGINE

	NUMBER OF CASES	PERCENTAGE
Successful Inductions	8	72.8
Failures	3	27.2

TABLE II. AVERAGE NUMBER OF DOSES USED TO INDUCE LABOR WITH FIVE MINIM DOSES OF METHERGINE

	NUMBER OF CASES	AVERAGE NUMBER OF DOSES USED TO INDUCE LABOR
Total	8	2 $\frac{1}{8}$
Primiparas	2	2 $\frac{1}{2}$
Multiparas	6	2
Primiparas with ruptured membranes	2	2 $\frac{1}{2}$
Multiparas with ruptured membranes	1	2
Multiparas with intact membranes	5	2

TABLE III. DEGREE OF EFFACEMENT OF CERVIX IN EIGHT SUCCESSFUL CASES INDUCED WITH FIVE MINIM DOSES OF METHERGINE

	PRIMIPARAS	MULTIPARAS
Uneffaced	2	3
Partially effaced (25%-50%)		3

was the size of a three months' gestation. The cervix was closed and uneffaced. The patient noted that there had been no increase in the size of the abdomen in the past three months. She was given 15 mg. stilbestrol in divided doses to sensitize the uterus, and then was given six doses of methergine of five minims each every hour. Following the last dose she went into labor and passed the fetus and placenta intact after a labor of one hour.

There were three cases of unsuccessful inductions in this group. The first case was a 32-year-old para i with intact membranes supposedly two weeks overdue. Rectal examination revealed the cervix to be closed, thick, and uneffaced. She was given six doses of methergine without any effect. She was discharged and was admitted subsequently two weeks later in active labor. She delivered a 6-pound, 11-ounce normal infant.

The second case was a 40-year-old primipara with membranes ruptured thirty-six hours. Rectal examination revealed a long, uneffaced, firm, closed cervix. She was given five doses of five minims each of methergine without any effect. Because of her age and rigidity of the cervix, a low cervical cesarean section was done and a living male infant was delivered weighing 6 pounds, 10 ounces.

The third case was a 32-year-old para i with intact membranes. Rectal examination revealed the cervix to be closed, thick, uneffaced and firm. She was given five doses of five minims each of methergine without any effect. She returned two weeks later with membranes rupturing spontaneously just before admission. At that time rectal examination revealed the cervix to be exactly the same as on her previous admission. She was given four 1 c.e. doses of methergine. She went into labor after the fourth dose and delivered forty-five minutes later.

The 1 c.e. dosage schedule was employed in 19 cases, all of which were successful.

Since the 1 c.e. dosage schedule gave uniformly successful results in all 19 patients in whom it was used with no ill effects it is considered to be the dosage of choice.

TABLE IV. DETAILS OF 19 SUCCESSFUL CASES

	NUMBER OF CASES	AVERAGE NUMBER OF DOSES TO INDUCE LABOR
Primiparas	8	2 $\frac{1}{2}$
Multiparas	11	3 $\frac{1}{3}$
Primiparas with ruptured membranes	2	2
Primiparas with intact membranes	6	2 $\frac{2}{3}$
Multiparas with ruptured membranes	6	3 $\frac{1}{3}$
Multiparas with intact membranes	5	3

TABLE V. DEGREE OF EFFACEMENT OF CERVIX IN 19 SUCCESSFUL CASES INDUCED WITH 1 C.C. DOSES OF METHERGINE

	PRIMIPARAS	MULTIPARAS
Uneffaced	3	6
Partially effaced (25%-50%)	2	1
Partially effaced (50%-75%)	1	2
Totally effaced	2	2

In the majority of cases more doses were given than required to induce labor. This was done to increase the strength and frequency of contractions. For example, if a patient went into labor after receiving two doses of methergine and her pains were ten minutes apart, she might be given an additional two or three doses until her pains became three or four minutes apart. When the patient was having pains every two to three minutes and the cervix was still uneffaced, the administration of 100 mg. demerol and $\frac{1}{150}$ grains scopolamine caused effacement and dilatation to proceed more rapidly with relief of pain to the parturient.

Maternal Effects

There were no untoward effects noted following the induction of labor with methergine. There was no material increase in blood pressure, pulse, or respirations. Methergine which is tasteless, colorless, and odorless was well tolerated. It did not evoke any nausea, vomiting, or other gastrointestinal disturbance. The postpartum course of those mothers who were induced with methergine was no different from those who went into labor spontaneously.

It was noted that the blood loss in the third stage appeared to be less with the methergine-induced cases than with those who went into labor spontaneously.

Methergine causes a marked increase in the tonicity of the uterus during labor, and it is believed that this tonicity of the uterus is carried over into the third stage after the expulsion of the placenta, thereby causing the uterus to remain well contracted. Since no accurate determination of blood loss was made, this observation will have to await further confirmation.

The effect on the uterus during the induction with methergine is striking. Usually the first effect that the mother will complain of is a steady suprapubic pressure. This pressure soon becomes severe enough to make the parturient feel uncomfortable. Within a short time, she begins to complain of backache and, if the uterus is carefully palpated at this time, it will be found to be contracting regularly with a marked degree of tonicity between contractions. This tonicity should not be interpreted as uterine tetany, as the uterus will be felt to relax somewhat between contractions. In the majority of cases, pains will occur soon after administration of methergine at intervals of two to three minutes. This is especially evident in patients with ruptured membranes, or in those in whom the cervix has become effaced. Once labor is initiated, the usual course is for it to progress rapidly, much more so than in those in whom no induction was done.

Effects on Fetus

There were no untoward effects upon the fetus. The fetal heart tones were not altered to any significant degree, in any case following the administration of methergine. All mothers induced with methergine bore normal infants and there were no neonatal deaths.

Effect on Length of Labor

In Table VII are listed those cases successfully induced with 1 c.c. doses of methergine. Included here is one case of frank breech in a primipara with intact membranes. This patient had a labor of seventeen and one-half hours. There was also one case of marginal placenta previa with intact membranes in a para i who had a labor of four hours and twenty-five minutes.

Beck¹² states that the length of labor averages twelve hours in a multipara and eighteen hours in a primipara. It will be seen from the figures in Tables VI and VII that the length of labor in both primiparas and multiparas has been markedly reduced.

TABLE VI. LENGTH OF LABOR WITH USE OF FIVE MINIM DOSES OF METHERGINE

	NUMBER OF CASES	AVERAGE LENGTH OF LABOR (HOURS)
Total	8	6¼
Primiparas	2	15
Multiparas	6	3½
Primiparas with ruptured membranes	2	15
Multiparas with ruptured membranes	1	2
Multiparas with intact membranes	5	3¾

TABLE VII. LENGTH OF LABOR WITH USE OF 1 C.C. DOSES OF METHERGINE

	NUMBER OF CASES	AVERAGE LENGTH OF LABOR (HOURS)
Total	19	6
Primiparas	8	6
Multiparas	11	6
Primiparas with ruptured membranes	2	4½
Primiparas with intact membranes	6	6½
Multiparas with ruptured membranes	6	3¾
Multiparas with intact membranes	5	9

The significance of these figures at once becomes apparent. In long drawn out labors with its attendant maternal exhaustion, postpartum hemorrhage is to be feared, because the uterus usually becomes atonic from exhaustion. Since methergine appears to have the ability to shorten labor when used for induction, it may also have value in shortening labor in uterine inertia and in long desultory type of labors with subsequent prevention of postpartum hemorrhage.

Comment

From the small number of cases presented, methergine appears to possess several advantages over the drugs and procedures in use at the present time for the induction of labor. Keeping the patient on her feet, castor oil, and the giving of enemas, although perfectly innocuous to both mother and infant, do not carry with them any fair degree of certainty that they will be successful. Quinine has been shown by King¹³ and Gelhorn¹⁴ to be the cause of fetal death,

and Taylor¹⁵ believes that quinine causes damage to the auditory nerves of the fetus. First¹⁶ states that the use of estrogens in large doses has been disappointing. Ergot and pituitary extract are unsuccessful in the majority of cases when the membranes are unruptured, and there are many cases in the literature of ruptured uteri due to the use of these drugs. Slemons¹⁷ combined intranasal pituitary extract with rupture of the membranes and obtained satisfactory results.

However, rupture of the membranes introduces a new factor to be seriously considered. If the membranes are ruptured and the medical induction with pituitary extract is successful, then all may be well; but, if the induction is unsuccessful and the membranes remain unruptured for twenty-four hours or more, the loss of amniotic fluid further complicates matters by adding the risk of amniotic sac infection, molding of the uterine, and intruterine asphyxia. Methergine, which appears to have the ability of inducing labor with intact as well as with ruptured membranes, would then be the drug of choice.

Tamponade of the lower uterine segment and vagina, or insertion of a hydrostatic bag or bougie all carry the added risk of infection with increase in morbidity, and, in addition, the hydrostatic bag causes displacement of the presenting part with possible prolapse of the cord.

Since methergine is an oxytocic, the same precautions should govern its use as with any other agent potent enough to cause uterine contractions. Theoretically, uterine tetany and rupture are possible, even though these serious complications were not observed in this series of cases. However, if uterine tetany should occur, the use of magnesium sulfate or magnesium gluconate intravenously as advocated by Abarbanel¹⁸ should abolish it immediately.

It is not the purpose of this paper to advocate routine induction of labor. Rather it is to set forth a method which will be relatively safe to mother and infant so that when the induction of labor is indicated we may be able to do so with safety and certainty. Under normal circumstances the spontaneous natural onset of labor is to be desired, but the indications previously set forth are in reality complications of pregnancy, and it may be injudicious to wait for labor to begin spontaneously under such circumstances. It is to be hoped that methergine, by helping to overcome some of our most trying complications of pregnancy, may become a safe and valuable addition to the obstetrician's armamentarium.

Conclusions

1. A new synthetic ergot preparation, methergine, was employed for the induction of labor in 30 consecutive cases in which satisfactory results were obtained in 27 instances.

2. Methergine was shown to have the ability to induce labor with intact as well as with ruptured membranes.

3. There were no maternal or fetal complications.

4. The length of labor is materially shortened in those cases induced with methergine.

5. Routine induction of labor is not advocated, and only those patients in whom a specific indication for induction exists should be considered candidates for induction.

6. Methergine may have considerable value in cases of uterine inertia.

Since this paper was written, 13 more inductions with methergine were done, 11 of which were successful.

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1829 PINE STREET

DIFFICULTIES AND ACCIDENTS ENCOUNTERED IN CONSTRUCTION OF THE VAGINA

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THERE are several methods of constructing the vagina. All of these have one technical point in common—the dissection of an adequate space. They differ chiefly in the manner or material by which this space is to be lined. The ultimate object of all these procedures is the same—the formation of a vagina that will allow normal sexual intercourse.

It is generally true that the more complicated and numerous the steps in an operation, the greater the number of possible accidents and complications. Most of the older operative techniques had one or more definite deficiencies—they were either complicated, presented technical difficulties, required a special knowledge of plastic surgery, involved long hospitalization, or were risky or uncertain in their outcome. Hence, very few vaginal constructions were carried out until simpler techniques were developed. The more recent procedures are not, of course, free from handicaps and risk; otherwise this article would not be written. But, with the elimination of many of the unfavorable features in the construction of the vagina, there has been a remarkable increase in the frequency with which this operation is being performed, and thus hundreds of women are now being enabled to lead a fairly normal sex life.

In general, two methods of construction of the vagina seem to have replaced the older, more complicated procedures: first, the technique first performed by the author in 1926 and published in 1938; and, second, the simpler procedure described by Frank in 1938. The former procedure is based on the principle first used by the author that the adult vaginal epithelium will proliferate and cover a dissected space, just as the embryonic vaginal epithelium proliferates and forms the vagina in the fetus. Using this principle, one merely dissects out the requisite space for the vagina and keeps it open by a suitable vaginal form; in time the epithelium from the vestibule or introitus will spread upward and cover the dissected space with normal vaginal epithelium.

Frank's operation is based on the principle that, in some young women, a space can be made between the urethra and rectum by firm, daily pressure of a hard tube, without any surgical dissection or anesthetic. Satisfactory vaginas have been made in this simple manner. This is the oldest of all methods of constructing the vagina, for a description of it was published more than one hundred years ago; and, probably twenty-five years ago, the late Dr. Howard A. Kelly remarked that he had seen a case in which the vagina had been made solely by the perseverance of the husband.

The techniques of both the author and Frank have been modified in many details. The most important modification of the author's technique has been

the use of skin grafts, usually Thiersch, to cover the form (Fig. 1). If the Thiersch graft does not take, it will slough out, and the existing vaginal epithelium at the introitus will proliferate and usually afford a functioning vagina. In both the author's and Frank's techniques, many varieties of forms and tubes have been devised and used; the authors themselves experimented with many such devices; it seems that any form works satisfactorily if it fulfills certain simple requirements.

Even with the simplest techniques, certain accidents and complications may develop, however, and it is with the avoidance and management of these difficulties that we are now concerned.

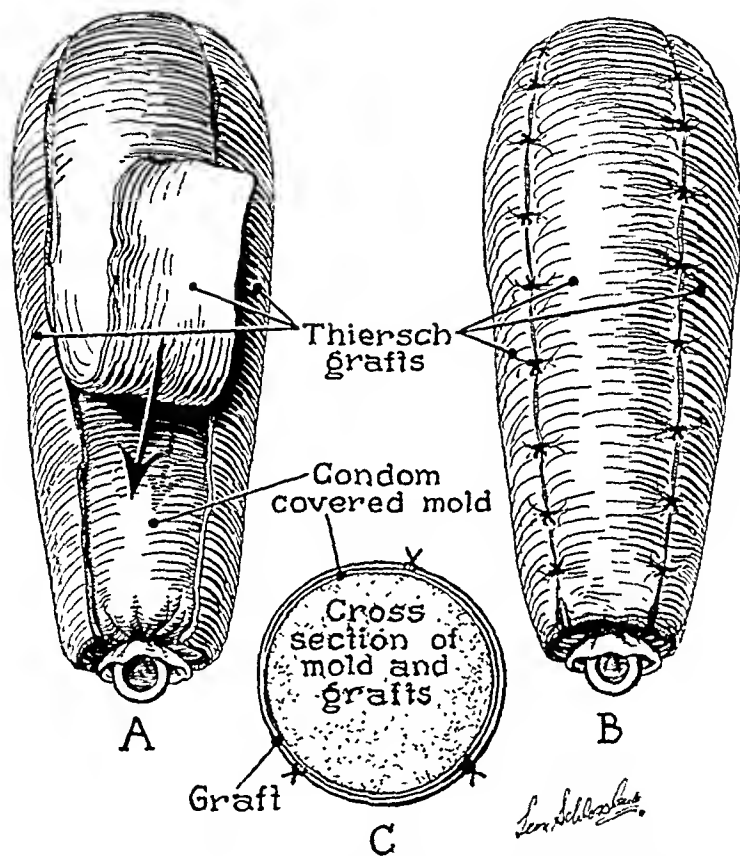


Fig. 1.—The vaginal form covered by Thiersch grafts. These are sewed on loosely, using the finest (0000) plain catgut sutures. A shows the graft partly sewed in place; B shows the graft completely fixed to the form. C is a cross section.

1. *The Prevention of Complications.*—Operative accidents and failures may be lessened, in the first place, by a wise choice of patients, performing the operation only in those cases in which it is likely to succeed. In general, it is best to construct vaginas only in women who are going to use them. If the constructed vagina is not used, it will probably contract just as the natural vagina does.

Our best results have been obtained in young women who have been recently married or are about to be. The ultimate result is liable to be questionable in older women who have never developed normal sex life, for, with advancing years, the sexual activities of both the husband and wife are apt to be on the wane.

The question arises whether one should construct the vagina in women who have no ovaries, or who have been deprived of ovarian function, or in male pseudohermaphrodites who have been brought up as females. The answer to these questions is found in the study of each individual patient. In young women who have no ovaries at all, a satisfactory vagina can be made and maintained if it is used often. Even in male pseudohermaphrodites, we have successfully made vaginas which have not contracted. Fig. 2 is a biopsy of a vagina made in a male pseudohermaphrodite who had been raised as a girl. It shows normal vaginal mucosa, which had grown up from the external genitals. The biopsy was taken three years after the construction of the vagina. The vagina was 6 cm. deep.



Fig. 2.—Biopsy of vaginal epithelium in a male pseudohermaphrodite who had been raised as a female. Vagina was constructed in September, 1941. Biopsy was taken in December, 1944, when the vagina admitted 3 fingers easily and was 6 cm. deep. This patient had no ovaries; had one normal testicle. Had used a good deal of stilbestrol to increase the size of "her" breasts, without permanent benefit. The vagina contracted to its present size soon after it had been made, because the form was worn irregularly. It has not contracted much if any in the last year, even though coitus has been very infrequent and forms have not been used. With Thiersch grafts, the result would undoubtedly have been better. (Gyn. Path. No. 61195.)

In the absence of ovaries, one can use Thiersch grafts, and thus avoid all dependence upon the proliferation of vaginal epithelium. Also, we have used estrogens in large doses in such cases to help maintain vaginal caliber and epithelium, but with very indifferent results. As a rule, in our experience, the chance of making and preserving a functioning vagina is distinctly less if ovarian function is absent or if the patient does not have normal sex life.

In deciding whether a vaginal construction is likely to be successful in any given case, the psychic and sexual attitudes of the patient are to be considered.

Many women with normal vaginas have unsatisfactory coitus and complain of dyspareunia because of nervous tension, hypersensitiveness, and sexual frigidity. If the patient with gynatresia also has these psychic and mental traits, the chance of success is distinctly decreased.

In the second place, the choice of the proper surgical procedure may in itself help avoid unnecessary difficulties. As a rule, the simpler the technique, the less the likelihood of something going wrong. Because of the complexity of the older operations, very few operations for construction of the vagina were attempted before the introduction of simpler, modern methods. Thus, before 1936, in a period of almost fifty years, the author is not able to find the record of a single operation for the construction of the vagina in the Johns Hopkins Hospital. Since then, in the past ten years since the introduction of simple methods, we have constructed sixteen vaginas. The same experience has been repeated in many of our large hospitals.

It seems to the author that the choice of operation lies between three procedures—the Frank procedure, the author's operation, or the operation of Graves. In young women who want to avoid a surgical procedure and who are patient enough to cooperate and persist for the required number of months, the Frank method may succeed, if the perineal tissues have enough elasticity to yield to the repeated pressure. But if the tissues are rigid, or if the patient is not placid enough to undergo the treatment, a surgical procedure may be necessary. It is certainly more direct and quicker.

Of the surgical procedures, the author has never tried any of the complicated operations, nor has he ever seen an instance in which they offered a better chance of success than the simpler ones. The Graves operation still is used occasionally, but it is difficult to visualize any advantage it offers over the simpler techniques.

The technique which the author has used is as follows: A transverse incision is made across the vestibule, where the opening of the vagina should be. If there is a rudimentary vagina, the incision is made across its vertex. A plane of cleavage is almost invariably found and can be followed without difficulty. As a rule, the vaginal space can be separated in five or ten minutes, largely by blunt dissection. In subsequent paragraphs, we shall discuss various problems that may arise in dissecting this space.

Having prepared the desired space, the proper vaginal form is then placed in it. Almost every gynecologist who has become interested in this problem has experimented with various types of vaginal forms and different materials for making them, just as we did. Hence, forms are now made of glass, vulcanized rubber, silver, Pyrex, various kinds of plastics, wood and other materials. We have used balsa wood forms in most of our recent cases because it is light, easily cut to any shape, and so cheap that one can keep a dozen or more forms ready at all times. They can be given to the patient. Each form is covered with a rubber condom, and sterilized by soaking in bichloride of mercury solution and then alcohol. A set of these forms is ready for use when one starts the operation and the appropriate size can be used in each case (Fig. 3).

We have used Thiersch grafts, as illustrated, for several years. These grafts are sewed over the form by interrupted sutures of the finest catgut (0000). The form is then inserted into the dissected space, and the operation is over. The form is not disturbed for three weeks; by that time the grafts should have taken strongly, and most of the vaginal walls should be firmly covered by healthy skin. The use of grafts hastens the covering of the vaginal walls and decreases the formation of scar tissue, which may develop with slower epithelization. If the grafts do not take, they will slough out, and there is an excellent chance that the vagina may then be covered by the spreading epithelium from the vaginal orifice, if the forms are kept in long enough.

An indwelling urethral catheter may be used or not, as one chooses. Recently, we have used a catheter in most of our cases, keeping it in the bladder for four or five days. The vaginal orifice must be large enough to avoid compressing the urethra between the pubis and the form; otherwise the terminal external urethra may slough.



Fig. 3.—The vaginal form. This particular form is made of balsa wood. The shape of the form tends to keep it in the vagina. One should use as large a form as can be worn comfortably. The end should protrude slightly from the vaginal orifice, so that it can be easily caught and removed. We use a small screw set in the end to permit easy handling. Mahorner has cut a groove in the upper surface, to avoid pressure on the urethra.

2. *The Dissection of an Adequate Space.*—Regardless of the choice of material or technique of operation, unless one dissects out a large vaginal space, the result will probably be disappointing. One should see to it that the space is deep (11 to 13 cm), wide, and that the vaginal orifice is big, admitting three fingers. During the months after operation, the walls tend to contract, and hence one must create a space larger than is really needed. After the vagina has been made and is covered by epithelium, it may get bigger and deeper with coitus; but this does not obviate the necessity of having an adequate space to begin with.

In dissecting out the space, one may encounter difficulties. At times, the plane of cleavage seems to end, for one runs into a smooth membrane which offers no break at all. In such cases, it is almost impossible to tell whether this wall that closes off the upper end of the space is the rectum, bladder, or peritoneum; also it is equally difficult to find any line of separation between these organs. In such a dilemma, several courses are open. One may have an assistant place a finger in the rectum, and a sound in the bladder; thus it may be possible to orient himself and avoid injuring these structures. At times, also, the plane of cleavage is found easily along the lateral edges of the dissec-

tion, near the pelvic wall. From this spot, the dissection can be then carried in safety toward the middle, and an adequate space created.

In patients who have not been operated upon before, this part of the operation is usually very easy and takes only five or ten minutes. But if the patient has had one or more former attempts at constructing a vagina, one is almost sure to face a difficult dissection. The plane of cleavage will be completely obliterated by dense scar tissue; every centimeter of space will be gained only by laborious sharp dissection. And at every step one runs the risk of entering the bladder or rectum. Such a dissection may take an hour or more. For this reason, the first man to operate upon the patient should know how to make a vagina and should use the proper technique at every step.

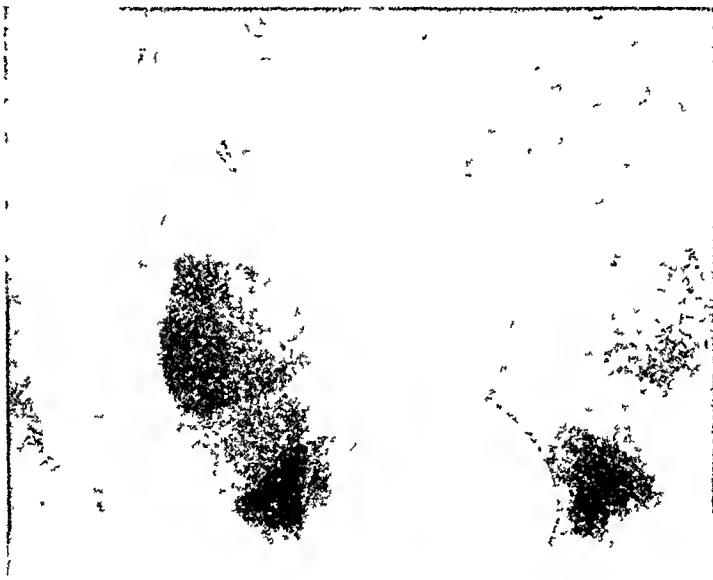


Fig. 4—A vaginogram, showing a constricting band. This may be due to lateral scar or to incomplete dissection in the region of the broad ligaments. The vagina functioned perfectly.

3. *Hemorrhage*.—Bleeding is not commonly encountered in dissecting out the vaginal space. If it is, it should be controlled completely, so that the grafts may lie on a dry surface. The points which are most liable to bleed are the lateral walls at the level of the broad ligaments. During the dissection, one can feel these structures like bands of thin ribbon. If they do not yield to blunt dissection, they must be cut. Otherwise they will constrict the vagina at that point and give the vagina an hourglass shape (see Fig. 4). Also, since these areas are vascular and convey the vaginal branches of the uterine vessels, they will bleed unless they are properly handled. Such vascular areas should be ligated by transfixion. Serious hemorrhage has occurred after operation from inadequate hemostasis in this region.

4. *Infection*.—It is surprising how rarely infection plays a part in this operation. Since the first operation which I performed for construction of the vagina in 1926, only one case has become infected. In this instance, the form

came out four or five hours after the operation, and fell into a bedpan. The patient picked up the form and reinserted it immediately, telling no one about the incident until she developed a purulent discharge and temperature of 102° F., two or three days later. We then removed the form, irrigated the vagina with boric acid solution, and replaced the sterilized form immediately. This procedure was carried out almost daily for a week or so, when the infection subsided. This complication did not interfere with the taking of the grafts, except in the apex. In this patient, five weeks later, the vagina was 13 cm. deep, and about 70 per cent covered by grafts.

The effect of an infection depends upon the technique that is used to make the vagina. If no grafts are used, and no foreign tissue is inserted at all, then the infection causes no significant trouble; it clears up quickly with irrigations and changing the form, producing little if any permanent damage. If Thiersch grafts are used, they may be lost, depending upon the severity of the infection and the promptness of treatment. If more complicated procedures are used, such as the infolding of split labia minora or other procedures, the damage may be greater. As a rule, however, plastic operations in this region heal very well.

Perforation of the Bladder or Rectum.—Perforation into the bladder or rectum may occur during the operation or later during the convalescence.

During the dissection of the vaginal space, there is not much danger of injuring the rectum or bladder if the plane of cleavage is normal and if the patient has not had a similar dissection before. Between the rectum and bladder, there is normally a well-defined plane of cleavage, which permits the operator to separate these organs largely by blunt dissection. This dissection can be usually carried up to the peritoneum of the cul-de-sac without any trouble at all. But, if the patient has had a former dissection in the region, a previous unsuccessful attempt to construct a vagina, then this plane of cleavage is replaced by scar tissue, and the rectum and bladder are glued to each other by dense fibrous tissue. Every moment of dissection, in such a case, is fraught with the danger of perforating the rectum or bladder; such dissections are always difficult, tedious, and long. Injuries to the bladder and rectum are common under these circumstances.

I have perforated the bladder wall in one such case. The opening was only a few millimeters in length, and was closed immediately, after which the vaginal dissection was completed. A retention catheter was placed, and the bladder healed almost completely. A tiny vesicovaginal fistula remained which leaked only a few drops in certain postures; in four or five months, this fistula healed spontaneously.

Rectal perforations are more annoying because they always introduce infection. Several such injuries have occurred, to my personal knowledge, although the literature records few, if any. We have not yet opened the rectum during the dissection of the vagina. In one instance, however, which the author reported before the Southern Surgical Association in 1944, the contractions of the abdominal and perineal muscles forced the end of the vaginal form through the apex of the vagina into the rectum five weeks after the operation. This

made a hole 4 or 5 cm. wide in the apex of the newly formed vagina, and transformed what appeared to be a perfect result into a possible disaster. We closed the fistula loosely by four or five interrupted sutures of 0 chromic catgut, packed the vagina loosely with xeroform gauze, and kept a large tube in the rectum for two weeks. The fistula closed completely, and one year later the patient had a large vagina 7 cm. deep. Although it had been 13 cm. deep, 7 cm. seemed satisfactory, especially since there had been no vagina before.

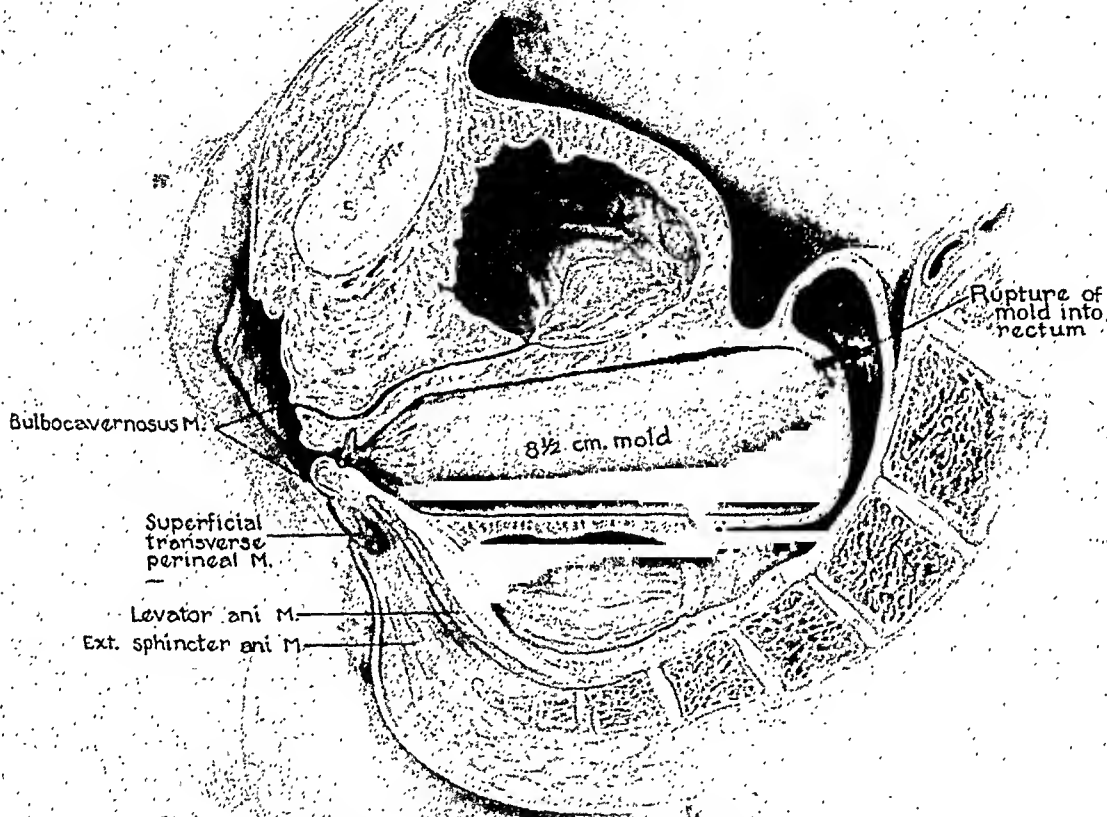


Fig. 5.—The possible danger of using a very small vaginal form. If the lower end of the form lies above the pelvic floor, downward pressure by the abdominal muscles and upward pressure of the pelvic floor may force it into the rectum. If the lower end of the form projects somewhat from the vagina, internal pressure will push it out of the vagina. (Courtesy of *Annals of Surgery*.)

Our concept of the mechanical situation which produced this unfortunate complication is shown in Fig. 5. The form which the patient was wearing at that time was very small—so short that the perineal muscles and vaginal orifice closed over it, and it disappeared completely in the vagina. It was thus not able to escape from the vaginal orifice when the abdominal and perineal pressure was increased. Hence, it was pushed back into the rectum. The perforation came when the patient became constipated and exerted strong abdominal pressure to have a stool.



Fig. 6.—A vaginogram, taken one year after construction of vagina. The vagina is 9 cm. deep, and commodious. Sexual intercourse was normal, with orgasm.

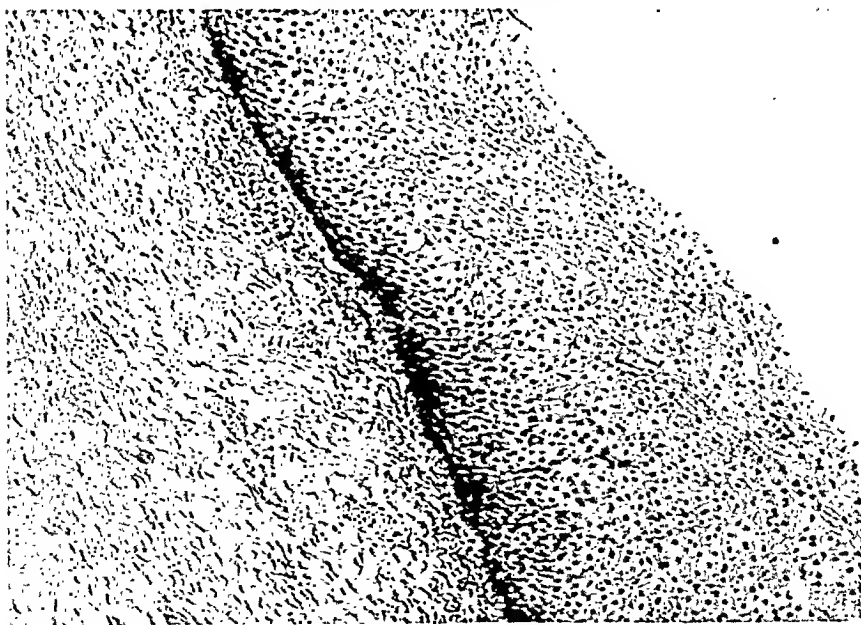


Fig. 7.—Biopsy of vaginal wall, one year after operation. Biopsy from apex of vagina, 9 cm. deep. No grafts were used in this case. This is normal vaginal epithelium.

On the basis of our experience, we think the form should be so long that it projects somewhat from the vaginal orifice. Also, the vaginal orifice should be large enough for the form to escape readily if the intrapelvic pressure is unduly increased.

The aftercare following construction of the vagina is simple. In uncomplicated cases, the form remains in the vagina three weeks. It is then removed and the vagina inspected and cleaned. The process of epithelization is observed, and a biopsy may be taken then if necessary. The form should be worn most of the time after that for another month, depending upon the progress of epithelization. After that it can be worn only part of the time, at night, if necessary. Coitus is begun carefully, after epithelization is firm and complete, usually in two months or less. Fig. 6 shows a vaginogram taken one year after operation—and Fig. 7, a biopsy of this vagina from a point 9 cm. above the external orifice. In this instance, the vagina actually became deeper as it was used.

Summary

In conclusion, we have presented a résumé of the common difficulties and complications that we have encountered in construction of the vagina.

In general, we recommend the simplest technique that is compatible with attaining a good result.

Care in the selection of patients as candidates for the operation will obviate some failures.

The dissection of a large space is essential. In patients who have had similar operations before, such dissections are always difficult and fraught with danger to the rectum and bladder.

We favor the use of Thiersch grafts to hasten epithelization.

Infection and hemorrhage rarely occur with proper precautions.

Perforation of the rectum or bladder may occur in the operating room or during convalescence. We have outlined precautions which should tend to obviate these accidents.

The postoperative care has been outlined.

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1201 NORTH CALVERT STREET.

THE DURATION OF GESTATION

With Special Reference to the Calculation of the Date of Delivery From Basal Temperature Graphs

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PERHAPS the most common misstatement of established fact in medicine is this: The period of gestation in woman is 10 lunar months, or 40 weeks, or 280 days. It is my purpose to draw attention to the essential fallacy of this statement, not to quibble over variations of a few days.

The normal menstrual cycle requires 28 days, and the normal interval from the last menses to delivery is 280 days. These facts require no corroboration. It has also been shown that ovulation usually occurs 14 days before menstruation, or, in the case of a woman with a 28-day cycle, 14 days after menstruation.

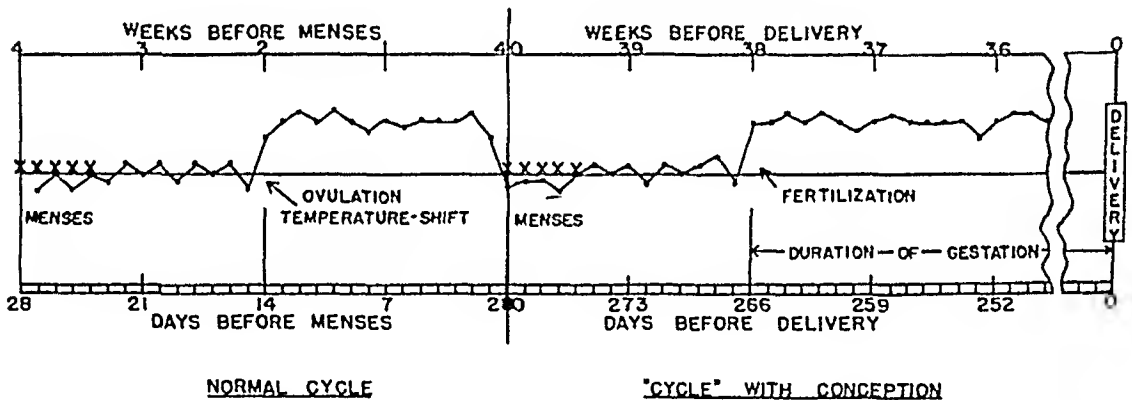


Fig. 1.—Idealized diagram of a temperature graph for a patient with a cycle of 28/5. The first portion of the graph shows the shift taking place in the basal body temperature graph near the time of ovulation which occurs just 14 days before menstruation in this theoretically normal individual, or 14 days after menstruation, since the cycle is exactly 28 days in length. In the second portion of the graph it is presumed that ovulation occurs at precisely the same interval after menstruation and that conception takes place. Since it is believed that fertilization of the ovum usually occurs during a brief period after ovulation (possibly 24 hours), it follows that the graphable indication of ovulation is also evidence of the approximate time of fertilization if the patient conceives. Furthermore, since the interval from the onset of the last menses to delivery is depleted as 280 days in the diagram, it is evident that the period of gestation is 266 days (38 weeks).

Fig. 2.—(Continued from opposite page.)

last menstrual period to actual delivery was counted; (2) the last menses were plotted on the chart; (3) the patient's graph was transcribed to the chart. It is often difficult to decide what degree of temperature variation constitutes a "temperature-shift." A rise of 0.4° F. or more above the average temperature for the preceding seven days seems to be a fairly reliable criterion. In Case 6 the first sharp rise is taken as the probable indication of ovulation and fertilization because coitus took place on that date and was not repeated during the ensuing five days. It will be noted that in every case the temperature-shift (believed to indicate the approximate time of ovulation and fertilization) occurred remarkably near the 266th day prior to delivery. Cases 8 and 10 show the greatest variation; these were the cases with premature rupture of the membranes. The temperature graphs were most helpful in predicting the date of delivery in the last four cases. (Case 7 is of unusual interest to those who concern themselves with treatment designed to stimulate ovulation; the entire graph for this patient may be found in the *J. Obst. & Gynaec. Brit. Emp.* 52: 252, 1945.)

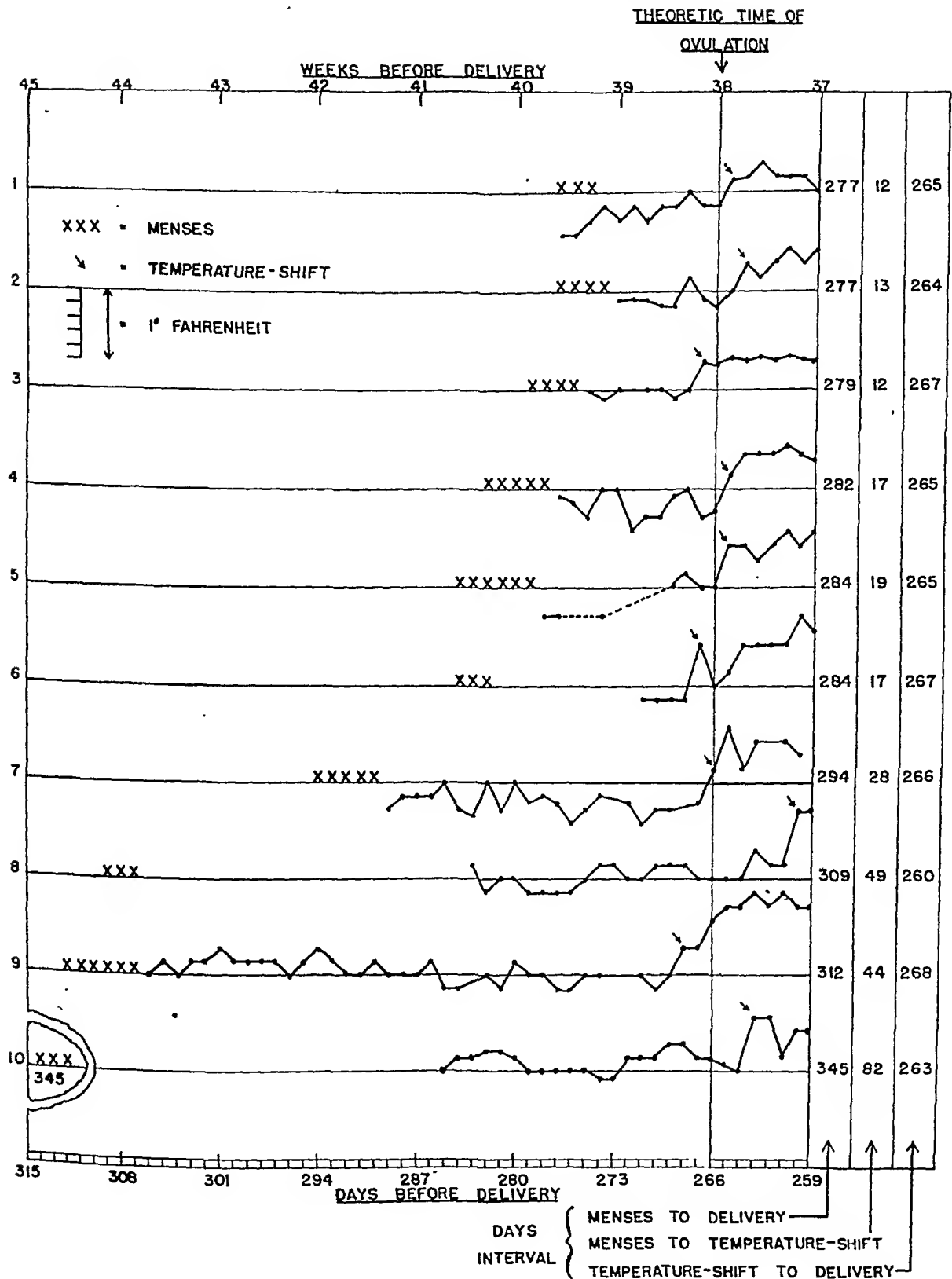


Fig. 2.—Presents 10 basal temperature graphs drawn by patients who conceived during the period covered by the graphs. The first six patients had menstrual cycles of about normal length (26 to 30 days), the last four patients had cycles varying from two to six months in length. All the patients fell into labor spontaneously, but in two cases the membranes ruptured spontaneously more than 24 hours before the onset of labor, which may have shortened the duration of these pregnancies somewhat. The exhibit above was compiled in three steps: (1) in each of the ten cases the number of days elapsing from the onset of the

(Legend continued on opposite page.)

Since fertilization cannot occur before ovulation (rare cases of ovarian pregnancy perhaps excepted), it is obvious that conception usually does not take place until about 14 days after menstruation. It therefore follows that the true period of gestation is 280 days minus 14 days, or 266 days (38 weeks). The point is not entirely academic, though it should be acknowledged in the interest of accuracy, but is of some practical importance to the obstetrician and may even be of interest to the legal profession.

Until recent years there were but two simple ways to calculate the probable date of delivery. The usual method, adding 280 days to the date of onset of the last menstrual period, is subject to several errors. The patient may not accurately recollect, or she may falsify the date of her last period, or she may mistake "implantation bleeding" for menstruation. Finally, this method of calculation is predicated upon the assumption that ovulation occurred 14 days after the beginning of the last period. In the case of the patient with regular 28-day cycles, this assumption is justifiable for the purpose of predicting the date of delivery. Nevertheless, it is an assumption which ordinarily cannot be proved, and therefore it is not a valid basis for determining the precise duration of gestation. It often happens that ovulation occurs many weeks after menstruation, a circumstance which probably explains the fabulous cases of "prolonged gestation" which are reported from time to time.

The duration of gestation may also be reckoned from the date of coitus, if intercourse took place infrequently and on known dates. In such instances the calculations are based entirely upon the patient's statements which in affairs of this sort are seldom, if ever, subject to indubitable confirmation. An objective indication of the date of ovulation and fertilization would be more acceptable to the scientific mind.

Such objective evidence is available in the form of daily temperature graphs. The onset of a sustained rise in the basal body temperature indicates the date of ovulation with considerable accuracy. Accordingly, whenever temperature graphs are available, one may determine the interval between ovulation and delivery by counting the days elapsing. Since fertilization of the ovum is believed to occur within a few hours after ovulation, the interval from ovulation to delivery is essentially the period of gestation. As has been pointed out, the duration of gestation is theoretically 266 days (Fig. 1). The period actually observed is astonishingly close to that predicted (Fig. 2).

Since gestation may be shortened by many factors, among them spontaneous rupture of the membranes, trauma, induction of labor (even by such simple means as castor oil taken with or without the physician's knowledge), polyhydramnios, and twins, no particular interest is attached to the matter of short pregnancies. A more interesting problem is the maximum duration of pregnancy.

In Fig. 2 are shown data from four patients in which the period of amenorrhea exceeded 290 days. In each instance the patient and her family felt that the baby was long overdue. Reference to the graphs shows that each of these patients ovulated more than two weeks after menstruation. When the delivery

date was calculated by adding 266 days to the date of ovulation as determined by the temperature graph, it was apparent that none of the patients was significantly overdue. The last four graphs in Fig. 2 represent all the cases which the author has seen in which pregnancy followed a late ovulation and terminated in spontaneous onset of labor. Other cases promised to be suitable for this presentation, but could not be included because the patient moved elsewhere, or had labor artificially induced or a cesarean section before the onset of labor. Even such a small series as this is collected largely by chance. When a larger series can be assembled, instances of true prolonged gestation will doubtless be found. Thus far the observations are in agreement with the idea that the normal duration of gestation is 38 weeks.

490 POST STREET

A TEN-YEAR SURVEY OF CESAREAN SECTION AT THE NEW HAVEN HOSPITAL

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A USEFUL method of evaluating surgical procedure is statistical study. This is particularly true of the operation of cesarean section, and recent analyses have shown not only an increased use of the operation, but also have revealed that the indications for its performance have been considerably widened. In any consideration of the results of cesarean section, as reported from various clinics, it should be borne in mind that, even in competent hands working in well-ordered institutions, variations in mortality and morbidity statistics are to be expected. This is due primarily to the types of obstetric cases which come to the hospital, and this, in turn, is usually an index to the kind of obstetrics that is practiced generally in the community which the hospital serves. A clinic which serves thickly settled urban areas of poor environment, where obstetric cases may be subject to neglect and may enter the hospital infected and late in labor, is bound to have its record affected adversely, regardless of competent subsequent treatment.

The present study includes 633 instances of cesarean section performed on the ward and private services of the New Haven Hospital over a 10-year period ending Dec. 31, 1944. The series is consecutive in that it includes all cases of cesarean section found in the cross-index file of the Record Department for the years 1935 to 1944 inclusive.

In the ward series for that period, there were 190 such operations in 6,238 deliveries, an incidence of 3.2 per cent. In the private series there were 443 operations in 4,580 deliveries, an incidence of 9.6 per cent. This difference in incidence in these two groups will be commented upon later.

Maternal Mortality

In the entire series there were two deaths, one in 1937 from hemorrhage and shock following a Latzko type section, and the other in 1942 as a result of incompatible blood transfusions, a gross mortality of 0.31 per cent, and a corrected mortality in so far as the operation itself is concerned of 0.15 per cent.

A summary of these two deaths follows:

CASE 1.—(Unit No. A 68625) 25-year-old white primigravida. Entered private service Feb. 10, 1937, with premature rupture of membranes. At the time of operation the indication for its performance was set down as, "Primiparous patient forty-eight hours in labor, with head floating, cervix 4 cm. dilated, normal pelvis, uterine inertia." Under ethylene anesthesia, a Latzko type operation was performed which was accompanied by a considerable amount of bleeding and surgical shock from which the patient expired five hours after operation.

CASE 2.—(Unit No. A 39583) 32-year-old white para iv, gravida v, admitted to ward service Aug. 16, 1942.

Previous Obstetric History.—

- a. In 1934, spontaneous delivery of normal female child, 3,050 grams.
- b. In 1935, spontaneous delivery of normal male child (term).
- c. In 1938, spontaneous delivery following medical induction for mild toxemia of male child, 3,650 grams, later jaundiced and said to have had blood dyscrasia.
- d. In 1939, precipitate delivery at eighth month of anencephalic monster.

At the time of the patient's entrance to the hospital in 1942 she was not in labor, but the abdomen showed extreme distention, no fetal parts were felt, and no fetal heart heard. Twelve hours after admission the membranes ruptured spontaneously and 4,500 c.c. of amniotic fluid escaped. Shortly after this occurred, the patient complained of weakness and dizziness, the blood pressure dropping from 158/94 on admission to 68/46, and the uterus becoming very tense and unrelaxing. The diagnosis of premature separation of the placenta with concealed hemorrhage was made. A classical cesarean section with tubal ligation was done after infusion had raised the blood pressure to 90/60. At operation a stillborn infant was delivered and the placenta was seen to be greatly enlarged and typically erythroblastotic. Inspection of the maternal surface showed a large area of old blood clots approximating one-third of the total surface of the placenta. Following the removal of infant and placenta, the uterus contracted well and the operation was completed expeditiously. The patient did not seem in good condition, although at the end of the operation the blood pressure was 108/60. Five hundred cubic centimeters of whole blood was given by transfusion on the table, and three hours later 500 c.c. of pooled plasma was similarly administered. Seven hours from the time of delivery 500 c.c. of whole blood was again given, and this was repeated nine hours after delivery, in all 2,000 c.c. of whole blood. Fifteen hours after delivery the patient had almost complete anuria, and death occurred twenty-nine hours after operation.

Autopsy findings on the mother showed hemorrhage into the peritoneal cavity, broad ligament, and left ovary, multiple foci of hemorrhage, and necrosis of liver, hemorrhage into glomeruli of kidney, generalized edema, icterus, congestion, and edema and atelectasis of lungs. Findings on the child showed erythroblastosis fetalis, hepatomegaly, splenomegaly, hypertrophy of heart, scattered intestinal hemorrhages, generalized edema, and ascites. (NOTE. It seems clear that incompatible blood transfusions caused this patient's death. At that time the laboratory determination of the Rh factor was not being done routinely on obstetric patients, as at present.)

Morbidity

In the ward series 29 per cent of patients showed a temperature rise to 100.4° F. or more some time during two 24-hour periods while in the hospital. In the private series, 19 per cent of the patients showed a similar rise. The difference in the two rates may possibly be explained by the more frequent taking of the temperature on the ward service as soon as any rise is noted.

Anesthesia

The following table gives the types of anesthesia for both services by years. An interesting shift from ethylene to cyclopropane and subsequently to pentothal is recorded.

TABLE I. TYPES OF OPERATION

WARD SERVICE	NUMBER
Classical	83
Low flap	74
Section followed by supravaginal hysterectomy	29
Extraperitoneal (Waters)	4
PRIVATE SERVICE	NUMBER
Classical	157
Low flap	252
Section followed by supravaginal hysterectomy	22
Extraperitoneal (Latzko and Waters)	12

TABLE II. TYPES OF ANESTHESIA. (BOTH SERVICES)

	ETHYLENE	CYCLO-PROPANE	ETHER	LOCAL	PENTOTHAL	SPINAL
1935	43	6	5	2	0	0
1936	30	6	7	2	0	0
1937	8	47	0	1	0	0
1938	0	35	2	0	0	1
1939	4	29	2	0	0	0
1940	2	63	1	3	0	1
1941	2	57	1	6	0	1
1942	3	87	0	5	10	0
1943	3	52	0	8	12	0
1944	7	19	0	1	62	0

TABLE III. PREDOMINANT INDICATION FOR OPERATION

	WARD	PRIVATE	TOTAL
Placenta previa	18	21	39
Premature separation of placenta	10	31	41
Disproportion	90	117	207
Toxemia of pregnancy	18	42	60
Uterine inertia	1	36	37
Previous cesarean section	20	85	105
Elderly primigravida	1	31	32
Myomas of uterus	3	9	12
Rheumatic heart disease	10	3	13
Previous repair of genital tract	1	7	8
Small pelvic outlet	0	3	3
Sterility	0	4	4
Primigravid breech	1	8	11
Single kidney	1	2	3
Tuberculosis (pulmonary)	1	1	2
Previous atony with postpartum hemorrhage	0	6	6
No stated indication	0	12	12
	175	418	593

Comment

In considering the relatively low corrected maternal mortality (one death from an operative procedure [Latzko] now superseded), it is interesting to speculate on some of the factors which may be said to be contributory. One of these has to do with the competence of those individuals who did the operations. In the ward service all operations were performed by the full-time staff of the hospital, either by the two senior members or the resident staff under supervision. In the private series the operations were performed by eleven

TABLE IV. MISCELLANEOUS

<i>Ward</i>	
Osteomyelitis of pelvis	1
Lymphogranuloma	2
Prolapse of cord	1
Ovarian cyst obstructing labor	2
Coarctation of aorta	1
Essential hypertension	3
Meningioma	1
Rupture of uterus	1
Persistent transverse	2
Primigravid breech	1
	<hr/> 15
<i>Private</i>	
Previous difficult labor	3
Ankylosis of hip	1
Asthenia	1
Previous removal of ovarian cyst	2
Previous myomectomy	1
Pernicious anemia	1
Severe anemia	1
Nonengagement of head	5
Prolapse of cord	1
Pyelitis (severe)	1
Ulcerative colitis	1
Cervical atresia	4
Fetal distress	1
Kyphosis	1
Habitual abortion	1
	<hr/> 25

individuals, all of whom are recognized specialists in the field of obstetrics and gynecology. Another factor previously mentioned has to do with the kind of clinical material which comes to this hospital. In the urban districts of Connecticut there is a very high rate of hospitalization for obstetric cases. Thus, in 1943, in the City of Hartford, 99.7 per cent of all births were in hospitals. In New Haven for 1944, 98.0 per cent of all deliveries were in hospitals. From this we can assume that in these and other urban areas of Connecticut the incidence of prenatal examinations is relatively high. This is probably true for the entire State, and this and the high rate of hospitalization are presumably considerable factors in limiting the deaths from puerperal causes for Connecticut in 1944 to 1.4 per 1,000 live births.

The greater incidence of the performance of cesarean section in the private series of this study is obviously influenced by many factors. Chief among these is the referral of obstetric cases showing complications to the specialist group by other physicians. Furthermore, it is well known that patients, having themselves had previous obstetric difficulties, seek out specialist care for subsequent delivery.

It is further interesting that 207, or 34.2 per cent, of operations on both services were done for disproportion. In this connection we point out that roentgen pelvimetry has been available and used by both groups. In the ward service this procedure has been part of the routine prenatal examination of every primigravid patient for practically the entire 10-year period. From our some-

what extended experience, we have for some time been convinced that, while a knowledge of the true capacity of the bony pelvis as revealed by x-ray may increase the incidence of cesarean section as an operation of choice over the difficult forceps or breech extraction, it is equally true that the employment of the operation will be decreased in such cases as unengaged head where disproportion is suspected but, when subjected to roentgen examination, does not actually exist. Stander reaches a somewhat similar conclusion and states, "As a result of x-ray pelvimetry the total incidence of cesarean section may not be markedly decreased, but this operative procedure should be performed more frequently upon correct indications, thus decreasing the unnecessary ones, at least these should be done more often at the proper time, instead of too late to be consistent with the best welfare of both mother and child."

To recapitulate, we have presented a summary of 633 cesarean sections performed on the ward and private services of the New Haven Hospital over a 10-year period. We have also discussed some of the influences which have contributed to a relatively low rate of mortality. In the series two deaths occurred, one after a type of operation (Latzko) now abandoned, and one as the result of incompatible transfusions, a gross mortality of 0.31 per cent and a corrected mortality of 0.15 per cent.

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FACIAL CHARACTERISTICS OF INFANTS WITH BILATERAL RENAL AGENESIS

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ONE has only to walk observantly through a nursery filled with infants a few hours or days old to realize how untrue is the oft-repeated statement that all newborn infants look alike. At the time of birth each has distinct facial characteristics which are easily discernible and which make it possible to identify each child.

Marked divergences from the normal facial contours, however, although not common at any age, are met with especial infrequency in the newborn period. Anencephalus, iniencephalus, and hydrocephalus are among the most common anomalies to produce definitely abnormal facies, but these are secondary to local disturbances in the formation of the cranial portion of the head. Fissures may produce marked distortion as a result of intrinsic abnormality in the development of the face. Partial duplication or absence or reduction in the size of any portion may also give a very unusual and bizarre appearance.

Other abnormalities may exist which have no known basis in any local structural development, but which produce a characteristic facial change. Mongolism is the best recognized member of this group and, although other concomitant divergences from normal are usually present to aid in making a diagnosis, the most striking abnormality is the facial expression.

Another condition having a characteristic facial appearance which has not been heretofore recognized is complete renal agenesis. The reason for the failure to observe the abnormality of the face probably lies in the small number of cases ordinarily seen by any one investigator. The author has now observed the faces of fifteen such infants* and all have been definitely abnormal. In examining the early cases, the fact that this change was specific to renal agenesis was not recognized, and the possibility that it constituted an unusual form of mongolism was considered. Further study has demonstrated, however, that the appearance differs markedly from that found in association with mongolism. Photographs of several of these infants show a remarkable inter-resemblance, and recently the absence of kidneys has been correctly prognosticated twice prior to examination of the interior of the body, because of the appearance of the face.

This facial expression has not been observed in association with death from any other cause. Infants with extreme renal hypoplasia or massive polycystic changes in the kidneys, all of whom die because of renal insufficiency, may have somewhat similar facies and may have some resemblance to infants with com-

*These and an additional five infants with renal agenesis are to be reported in detail at a later date.

plete renal agenesis, but the appearance is never as typical, and the presence of a kidney anomaly cannot be foretold with certainty.

The most striking feature consists of an increase in width between the eyes and the presence of an unusually prominent fold arising at the inner canthus of each eye (Figs. 1, 2, and 3). The fold sweeps downward and laterally to



Fig. 1.—Characteristic facies. No anomalies except renal agenesis. Age at death: 44 minutes.



Fig. 2.—Characteristic facies. In addition to renal agenesis the infant exhibited an imperforate anus, absence of uterus and vagina, and contractures of hips and elbows. Age at death: 25 minutes.

form a wide semicircle under the inferior medial aspect of each orbital space. Other changes which, when combined with the appearance of the eyes, gives the face of the infant a resemblance to that of a person of very advanced age—an extreme premature senility, as it were—are a flattening and slight broadening



Fig. 3.—Characteristic facies. The suprarrenal glands are flat discs lying against the posterior abdominal wall. The Fallopian tubes are present; uterus and vagina are absent. Associated anomalies consisted of malrotation of the intestine and hypoplasia of the spleen. Age at death: 59 minutes.

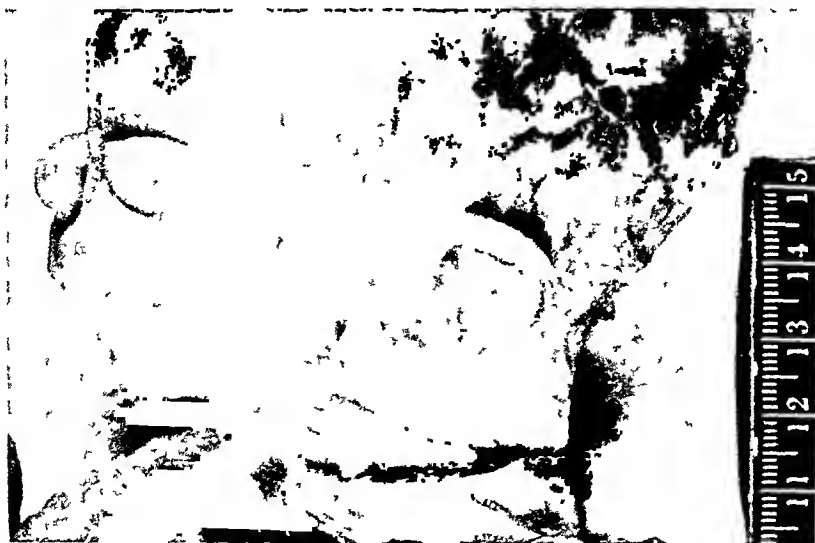


Fig. 4.—Characteristic facies. The low-lying, large, flat ears are well shown. No associated anomalies except clubbed feet. Age at death: 2 hours and 15 minutes.

of the nose, an unusually receding chin, and large, low-set ears which have proportionately little cartilage (Fig. 4).

The statement has been made that complete renal agenesis never exists except in association with gross external and internal anomalies. This is true if the facial appearance is considered a gross anomaly, but, although the change is constant, it cannot accurately be considered a malformation. In addition to the facial disturbance, there was no departure from the normal which could be discerned on external examination in three of these infants, and no abnormality except clubfoot in an additional four. The cause of death assigned to all but six of the fifteen infants prior to postmortem examination was intrauterine asphyxia or birth trauma.

The outlook for infants with renal agenesis is hopeless, regardless of whether or not the condition is recognized prior to necropsy, and the establishment of an accurate diagnosis in these cases is of little importance to the parents in relation to future procreation. It is of value, however, to establish as completely as possible the cause of death in every infant who fails to make a satisfactory adjustment to its extruterine environment, and the recognition of this facial expression may aid in arriving at a diagnosis in at least an occasional infant.

There are a few other conditions such as osteopetrosis and hypertelorism which are sometimes recognizable from the faces of newborn infants but which do not produce their major disturbances until years later. If careful examination of the face and facial expression were to be made part of the routine physical examination of all infants, it seems probable that facies characteristic of still other conditions might be recognized.

Summary

Bilateral renal agenesis is associated with a type of facies so characteristic that the absence of kidneys can be diagnosed in most instances on this finding alone. The principal change consists of a mild increase in width between the eyes, a very prominent fold of skin arising at the inner canthus, a flattening of the nose, mild retraction of the lower jaw, and large, low-lying ears with incomplete cartilaginous development.

CHIARI-FROMMEL SYNDROME

An Historical Review With Case Report

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INFREQUENTLY, cases of the rare syndrome of atrophy of the uterus and ovaries associated with persistent lactation have been reported since the time of Chiari, who, in collaboration with C. Braun and J. Spaeth, published a series of essays covering gynecologic and obstetric data during the years 1848 to 1855. In one section of these essays, Chiari gave a description of two cases of puerperal uteroovarian atrophy accompanied by persistent lactation. He believed both of these cases to be early senile atrophy of the uterus, and were dependent upon the nutritional status of the patient being more or less influenced by general health factors.

Frommel, in 1882, gave an exhaustive description of this syndrome. He investigated 3,000 labors and puerpera, and arrived at the conclusion that the incidence of uterine atrophy was not more than 1 per cent. In his cases, the ages of the patients exhibiting the syndrome varied between 19 and 40 years, the average being 29.6 years. A slightly abridged translation of his report, taken from Sharp's article, gives an accurate description of this puerperal syndrome: "As a rule the women are young and poorly nourished and at first glance do not appear to be in their twentieth year. They come to the physician not because of amenorrhea, despite the fact that breast feeding has been discontinued for several months, but because of a great number of complaints. Abdominal pain, sensations of active movements in the abdomen, backache over the entire back and extending down both legs, and numerous hysterical manifestations are among the symptoms. They are distressed and show mental depression.

"The inspection of the external genitalia is, as a rule, negative. No inflammatory changes are present in the uterine adnexa, the ovaries are free and movable, but uterine atrophy is always found. In a few cases the uterus is much smaller, extraordinarily thin, length decreased (5 to 5.5 cm., in one case only 4.5 cm.) and generally firm and palpable. The atrophy affects the cervix, also, which is visible as a small peg in the vagina, or, similar to senile atrophy, may be entirely absent. In other cases the uterus is not shortened, but there is a change in the thickness of the walls, so that palpation is often difficult. The uterine body is generally mobile and can be moved from the anteverted to the retroverted position, but this type is usually in the retroposition. The vaginal cervix is often thick and firm, but sometimes atrophic and flaccid. In introducing instruments, care must be exercised to prevent piercing the uterine walls.

"In the majority of cases the ovaries are small and atrophic. Only three cases out of twenty-eight showed ovaries of normal size. Menstruation did not reappear in all cases after weaning. In one case the menses resumed for a short time, but amenorrhea ensued. The condition may be caused or at least aggravated by lactation."

In his conclusions, Frommel stated that women who experience numerous pregnancies in rapid sequence impose a great demand on the genital organs which may lead to uterine atrophy. He recommended prophylaxis, detection of

The patient was seen on April 30, 1945. Her last menstrual period occurred on April 21, and was of five days' duration. Physical examination was essentially the same as at the previous visit. A Wassermann taken at this time was reported weakly positive. She was seen again March 29, 1946, and stated that her periods had been regular every twenty-eight days for the past year.

Summary

1. An historical review of the literature on the Chiari-Frommel syndrome is presented.
2. A case of this syndrome is reported, with treatment with stilbestrol.

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3520 FAIRMOUNT STREET

HETEROLOGOUS TRANSPLANTATION OF HUMAN MALIGNANT OVARIAN TUMOR

Report of Successful Growth of Human Papillary Cystadenocarcinoma in Anterior Chamber of Eye of Guinea Pig

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MALIGNANT tumors of the ovary account for about 10 per cent of the malignancies in the human female generative tract. Their morphology is quite diverse, and many of the tumors are of infrequent occurrence. This has led to considerable difference of opinion in establishing the classification and postulating the etiology of specific tumors.¹ Furthermore, the course of the disease which ovarian carcinomas produce often is one of extreme torture, and the outcome is usually fatal. Therefore, any new approach to their study seems worth recording. No successful transplants of these tumors have been reported, save one of pseudomucinous cystadenocarcinoma (reported by Zondek) which microscopically consisted only of pseudomucinous material and "a striking scarcity of cells."² In this preliminary report we present gross and microscopic evidence of successful transplantation of a papillary cystadenocarcinoma of the ovary. Further studies of morphology and physiology of transplanted ovarian tumors are being conducted and will appear later. The approach we have used is one which gynecologic surgeons and pathologists may find useful in studying malignant ovarian tumors.

Materials and Methods

The methods we used were those which Greene has found highly successful in tumor transplantation.^{3, 4} The details of technique may be found in his articles, and those who plan to use the anterior chamber method of tissue culture should study Greene's contributions carefully. We have observed in particular the following facts he has listed:

1. Growth has been more successful in guinea pig anterior chamber than in any other animals.
2. Only tumors which show ability to invade adjacent tissues have been very successful in transplantation.
3. The portion of tumor used should be kept as sterile as possible and should be transplanted within a few hours, although takes have been successful up to twenty-four hours after removal from the host.
4. Vascularity and increase in size of transplant are evidences of growth. This usually occurs in from two weeks to two months, but occasionally not until six months after implantation.
5. Spontaneous regression may follow the phase of tumor growth.
6. After successful primary transplantation and growth in the anterior chamber, transfer to other regions is readily effected.

Pieces of tumor tissue over 2 mm. in diameter were introduced into the anterior chamber of the eye of guinea pigs through an opening made in the cornea. This was accomplished with as little trauma to the tumor and eye as possible.

Case Report

History.—E. D., a 60-year-old white woman (patient of Dr. Roy Fallas) complained of bloating and increase in size of the abdomen during six months preceding first examination. There had been slight weight loss, but no other symptoms. System review and past history were unimportant. The patient had menstruated regularly until the age of 50, and there had been no bleeding or discharge since that time.

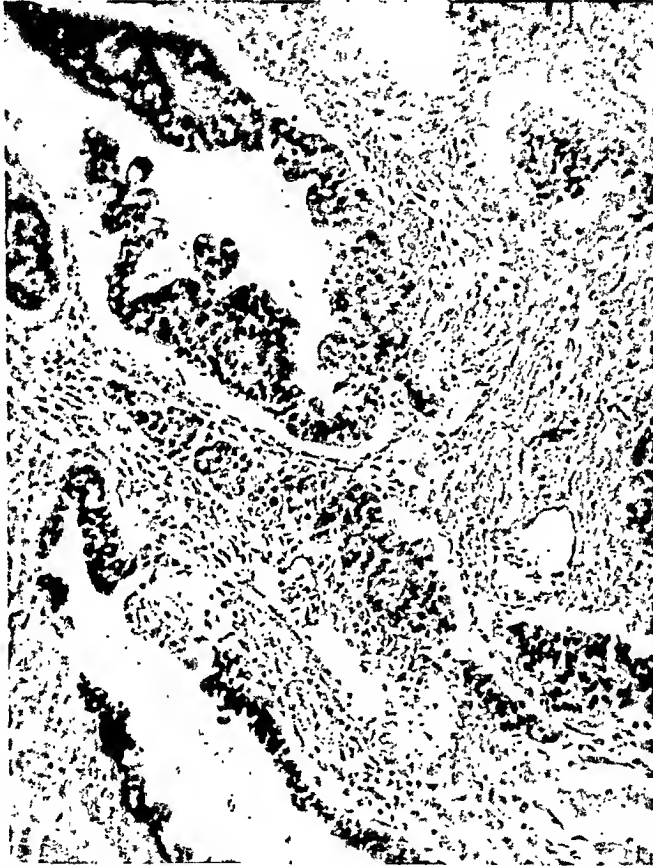


Fig. 1.—Section of ovarian tissue removed at operation. The cyst spaces and papillary projections of epithellum established this as a papillary cystadenocarcinoma ($\times 125$).

Physical examination revealed a well-nourished woman whose abdomen was greatly distended. Ascites was easily demonstrated by the usual physical changes. At operation, the omentum was found to be thick and cartilaginous as a result of metastatic tumor involvement. The mesentery of the bowel was studded with small papillary implants, and the ovary was found to be the site of a tumor which had extended throughout the pelvic structures so that removal was impossible. A piece of ovary 2.5 by 2 by 1 cm. was removed manually. Its external surface was finely nodular, translucent, and gray. On surfaces made by sectioning, cystic spaces with fairly smooth lining were seen. Small areas of tissue on the lining had a papillary appearance.

Histologic Examination.—(Fig. 1.) The ovarian tissue was completely replaced by tumor. In some areas the cells were arranged in loose irregular masses, separated by a stroma almost myxomatous in appearance. In other areas the tumor cells were arranged around central spaces. Some of these spaces contained a serous type of fluid that took a



Fig. 2.—Ovarian transplant with cornea and iris of guinea pig, adjacent to tumor. Vessels of the tumor and the suggestion of glandular arrangement are easily seen. Transplant is seven weeks old. Diagnosis: adenocarcinoma.

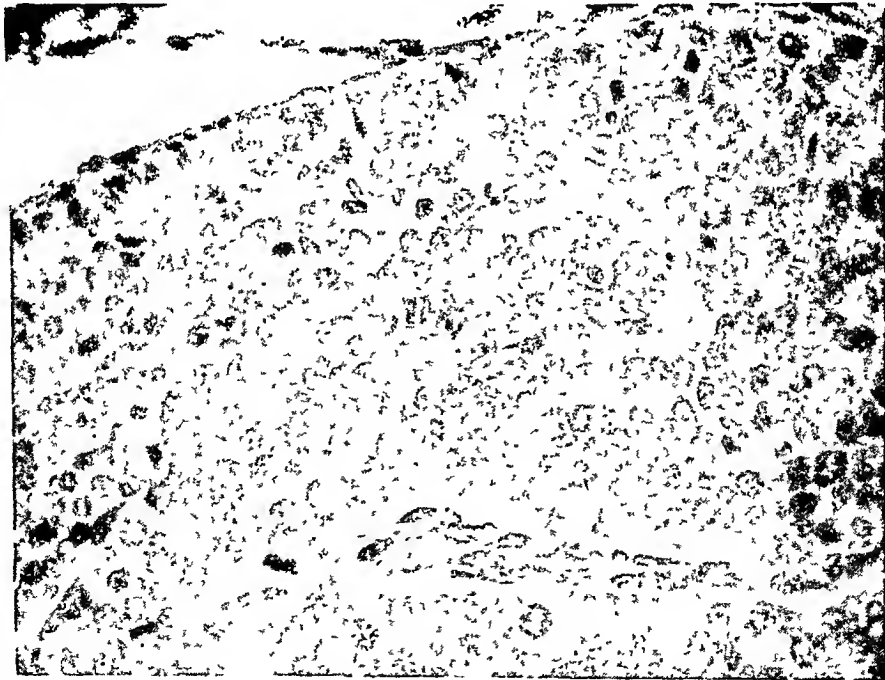


Fig. 3.—Higher power of ovarian transplant. Mitotic figures and vascular supply prove that the tumor is growing ($\times 475$).

pale eosin stain. The lining consisted of several layers of tumor cells, or, in the larger cysts, of a single layer of columnar epithelium. In the larger cystic spaces the epithelium was thrown into papillary folds. Most of the cells were elongated and contained an oval vesicular nucleus. Hyperchromatic nuclei and mitoses were frequent.

Diagnosis.—Papillary cystadenocarcinoma of the ovary, serous type.

Transplantation Study

The tumor removed had not been kept entirely sterile, but a piece of it was placed in sterile normal saline solution saturated with sulfathiazole crystals. Transplantation was made into the anterior chamber of the eye of guinea pigs under ether anesthesia within three hours after the tumor was removed. Vascularization of the tumor in the anterior chamber, manifested by its newly acquired pink color, was first noted in one guinea pig within five weeks after transplantation. Within six and one-half weeks this tumor had reached a size of 4 by 6 mm. When examined under a slit lamp the tumor resembled, to some degree, the yolk of an egg, and large vessels could be seen entering it.

Histologic Examination.—(Figs. 2 and 3.) The tumor had a slightly adenomatous appearance but was generally solid, and the cells were rather undifferentiated. There were two spaces containing a few free cells. These, perhaps, were the beginning of cysts, but no other cystic areas were present. There were no papillary projections, and there was little connective tissue stroma. Hyperchromatic nuclei and mitoses were less than in the primary tumor. The tumor was surrounded by a thin capsule and the vascular supply was easily visible. Sections through other parts of the tumor were similar to that seen in Figs. 2 and 3.

Diagnosis.—Adenocarcinoma.

Comment

A tumor of the adenocarcinoma type has been grown in the eye of a guinea pig as a result of transplanting a human papillary cystadenocarcinoma of the ovary into the anterior chamber of the eye in the experimental animal. This demonstrates clearly that malignant tumors of the human ovary can be transplanted into other species where they will survive and grow. The method may prove valuable in studying the morphology and physiology of ovarian tumors, and in determining their etiology.

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EXTRAMEMBRANOUS PREGNANCY*

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FOLLOWING early rupture of the membranes the uterus does not always empty itself promptly. Instead, in rare instances the fetus develops for a variable time outside the collapsed membranes and thus free in the uterine cavity. Meanwhile the production of amniotic fluid continues. Such an extramembranous or extrachorionic pregnancy has been known to persist for as long as one hundred and twenty days.¹ Although some cases are no doubt not recognized and others go unreported, the fact that in 1939 Alfonso² found only about 50 case reports in the literature is evidence that the condition is quite rare. Strangely, most of the articles to be found are in French or from South America, with only a few in German. In this country the textbooks by both Williams and DeLee make mention of extramembranous pregnancy, but I have been unable to trace a single case reported in the English language during the last twenty years. Besides its rarity, this abnormality is of interest because of etiological and diagnostic problems, its effect on the child, and its possible relationship to some other conditions.

Case Report

Patient 23 years of age. The first pregnancy ended in full-term delivery in October, 1940. A second terminated five weeks prematurely in February, 1944, following premature rupture of the membranes. Both children are living and well. The past history otherwise was unessential. In all pregnancies the Kahn test was negative for syphilis.

The last menstrual period was Nov. 18, 1944, the calculated expected date of delivery being Aug. 25, 1945. During January and February there was slight vaginal bleeding for a few days on several occasions. On March 21 (between seventeen and eighteen weeks after the last regular menstrual period), the patient reported a gush of clear fluid from the vagina. The loss of fluid then continued intermittently until delivery, either in sudden large amounts or as a continuous trickle for periods of several days. There was also bleeding occasionally, but this was never of consequence as evidenced by the fact that moderate anemia early in pregnancy steadily improved with therapy and a fairly normal hemoglobin was maintained. The pregnancy continued otherwise uneventfully until the onset of labor and spontaneous premature delivery on June 19, 1945, approximately nine weeks before term. The apparently normally developed male child, weighing 4 pounds, 1 ounce, lived only two hours. Important postmortem findings were as follows: atelectasis of right lung with partial atelectasis of the left; patent ductus arteriosus, and foramen ovale.

The placenta was of particular interest. It measured 14 by 13.5 by 2.5 cm. and weighed 330 grams. As shown in Fig. 1, the fetal surface was only partially covered by the placental portion of the sac (the area measuring 10 by 10 cm.), the uncovered margin thus giving resemblance to the condition of placenta circumvallata. This will be referred to later. The umbilical cord was inserted centrally and was 43 cm. in length. The membranous sac had a large, ragged

*Presented at a meeting of the Michigan Society of Obstetricians and Gynecologists, Oct. 1, 1945.

opening, the longest and shortest distances from its edges to the placenta being 8 and 2 cm., respectively. By elevating the circumference of this opening with forceps it was possible to fully distend the amniotic cavity with water. The capacity was 450 c.c. which was obviously much too small to accommodate the 4-pound, 1-ounce (1,800-gram) fetus, but it did approximate that of a pregnancy at the time (sixteen to eighteen weeks) of rupture of the membranes. Microscopic examination showed only very slight leucocytic infiltration of the placental chorion, the villi and umbilical cord being essentially normal.



Fig. 1.—Extramembranous development of the fetus, showing the relatively small size of the membranous sac as compared to the fetus. Margin of placenta is uncovered by membranes.

Consideration of the etiology of extramembranous pregnancy concerns first of all the various possible causes of early rupture of the membranes. Alfonso² has listed these, of which the most important are: external trauma; internal trauma (coitus, uterine curettage, attempts at abortion); hydramnios with excessive distention; oligohydramnios with close contraction of the membranes around the fetus so that its movements cause rupture; inflammation with consequent weakening and friability of the membranes; anomalies in form or position of the uterus; and tumors of the uterus such as uterine polyps. Koenig³ reported an example following an attempt at abortion by medication with mugwort. Voglino's⁴ interesting case occurred following curettage on a diagnosis of inevitable abortion, the possibilities being either that the defective ovum was not removed and continued to develop, or that a twin ovum in a horn of the

"anvil shaped" uterus persisted, though damaged. In many instances, however, as in the one described above, the cause is uncertain. The other consideration in the etiology, i.e., the question as to why the damaged ovum should sometimes be retained in the uterus, is up to the present time a matter of pure conjecture.

The diagnosis of extramembranous pregnancy depends primarily on the persistent loss of fluid. It may apparently be confused with the likewise very rare condition of *hydorrhea gravidarum*, a situation in which there is for some unexplained reason a marked secretion from the decidual glands. In this case the secreted fluid is often discharged intermittently, whereas, in the other the fluid comes away more or less ceaselessly. Also, with extramembranous pregnancy there is usually bleeding from time to time. Moreover, examination of the fluid is said to show *vernix caseosa*, lanugo hairs, and constituents of fetal urine, though in Koenig's³ case this was not true. Such signs as that of a smaller than expected uterus or a tenseness of the uterine wall over the fetus were not noticeable in my case. Actually, it would appear that many times a positive diagnosis cannot be made until after delivery, even though suspected.

Contrary to what might be expected, extramembranous pregnancy seldom leads to antepartum and postpartum infection, even though the membranous barrier to the entrance of bacteria into the uterus is lost. Sometimes, however, there are profuse or repeated hemorrhages which necessitate interruption of pregnancy, as apparently occurred in the case of Morgantini and Balaguer,⁵ but this is about the only maternal circumstance which demands special consideration or treatment. For the child the prognosis is not so good. Premature delivery is the rule, and deformities are frequent, though not universal. In my case they were absent. The abnormalities encountered result from pressure in the absence of amniotic fluid, and as Hückel⁶ pointed out, are not the same as the amputations and other mutilations from amniotic adhesions which often accompany extra-amniotic development after rupture and collapse of the amnion, but with the outer chorionic membrane remaining intact.

The condition of extra-amniotic pregnancy, though often confused with extramembranous pregnancy, is a distinct entity. However, at least one author (Meyer-Rüegg)⁷ suspected that there was an etiological relationship in the sense that the first abnormality may sometimes result from the second. He postulated that early in pregnancy a rupture of the two membranes before they had become adherent to each other would, of course, permit complete collapse of the amnion. The chorion, on the other hand, being attached somewhat to the uterine wall could conceivably remain uncollapsed, thus offering a situation for possible healing of the tear with the fetus then lying extra-annially, but still within the chorionic sac.

At one time extramembranous pregnancy was also thought to have some relationship to *placenta circumvallata*, often called *marginata*. However, in 1927 Williams' careful study of *placenta circumvallata*⁸ gave rather convincing evidence that the resemblance of the placentas in the two conditions was a superficial one only, though he could not from personal knowledge be sure of this as he had had little experience with extramembranous pregnancy. In both cases the membranes may arise well within the circumference of the placenta, thus leaving an outer ring or margin on the fetal surface uncovered by membranes. In extramembranous pregnancy this appearance is due to an actually smaller amnion and chorion-covered area or plate, the remaining margin being covered only by a layer of decidual cells mingled with more or less hyalinized fibrin. This structural arrangement was clearly demonstrated by microscopic examination of sections from my case. In *placenta circumvallata* the membranes actually continue out toward the edge of the placenta as usual, but then for some not well-explained reason they turn and double back over themselves

for a distance toward the center of the placenta. Where this reduplication ends, the membranes are there given off to extend around the uterine cavity and make up the fetal sac. Usually the place of apparent origin of the membranes is rounded or oval and encloses a slightly depressed amnion-covered area, with an uncovered ring or marginal area outside just as in extramembranous pregnancy. In many instances it is quite possible that the different arrangement of the membranes in the two conditions could be distinguished with certainty only by microscopic examination. It also seems possible that some of the difficulties (such as abortion or premature labor, and unexplained bleeding) ascribed in the past to placenta circumvallata were actually due to erroneously included extramembranous pregnancy cases.

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955 FISHER BUILDING

HYDATIDIFORM MOLE WITH SEVERE PRE-ECLAMPSIA

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IN THE obstetric literature there is but sporadic reference to the association of pregnancy toxemia with chorionic molar degeneration. In his discussion of hydatidiform mole Irving¹ states that "three of our 19 patients studied in recent years had pre-eclampsia and one had eclampsia, which is in keeping with the known fact that the condition (hydatidiform mole) may be accompanied by albuminuria, hypertension, and edema." Greenhill² editorially comments that "signs of toxemia, particularly nausea and vomiting, constitute an important clue to the presence of hydatidiform mole. Toxemia without mole rarely occurs in the early months of pregnancy." Sherman,³ in his study of 78 patients with hydatidiform mole, remarks that "nausea, vomiting, and toxic manifestations occurred so often and with such propensity, that a diagnosis of either hyperemesis gravidarum or toxemia of pregnancy was made in a large number of patients." There was an accompanying hyperemesis gravidarum or toxemia of pregnancy in 29.4 per cent of the patients in Sherman's series. In his article on hydatidiform mole, Brews⁴ remarks that "the presence of signs of pregnancy toxemia at an unusually early period of gestation may be of significance." In 37 per cent of Brews' 56 cases albuminuria was present. Recently an instance of fulminating severe pre-eclampsia complicating hydatidiform mole was seen on the Obstetrical Service of University Hospitals. Inasmuch as the toxemia was so severe, and inasmuch as the response to evacuation of the uterus was so prompt, the clinical experience was considered worthy of publication.

Case Report

E. E. (No. 64-262), a 22-year-old Negro woman, gravida iii, para ii, registered in the Prenatal Clinic of University Hospitals on Nov. 28, 1944. The last menstrual period began on July 23, 1944. Aside from syphilis during the patient's second pregnancy, for which adequate treatment had been given, the past history was not remarkable. The previous labors and puerperia had not been abnormal. The medical history revealed that in September, 1943, the blood pressure was 118/80, and the urine was negative for albumin. The patient was not seen for ten months, during which time she was quite well. In July, 1944, the blood pressure, as obtained at Lakeside Outpatient Department, was 106/80. When, on Nov. 13, 1944, the patient was seen in Lakeside Emergency Ward, because of some vaginal spotting, the blood pressure was recorded at 150/90, and the urine was free of albumin. The patient was admitted to Maternity Hospital on Nov. 29, 1944, because of hypertension detected on the previous day in the Prenatal Clinic. On admission to the hospital, the patient complained of "weakness and swelling of the legs." The patient recalled having had vaginal spotting during the previous two months. The blood pressure on admission was 190/140. The patient did not appear acutely or chronically ill. The ocular fundi were normal. There was a systolic murmur over the apex, but the heart was not enlarged. The lungs were clear. There was moderate pitting edema of both ankles. The tendon reflexes were hypoactive but equal, and there were no cranial nerve palsies. On obstetric examination, the outlet was relaxed, and the cervix patulous. The fundus uteri was symmetrically

enlarged, to the size of a six months' gestation. The adnexa were normal. Neither fetal heart tones nor fetal movements could be detected.

Laboratory Studies.—Catheterized urine, on admission, was acid in reaction, and contained 6 Gm. of albumin; sediment was loaded with hyaline and granular casts, and there were some red blood cells. The Rh factor was positive. Hemoglobin was 74 per cent (Sahli); erythrocytes numbered 4,250,000, and leucocytes, 8,100. There was no azotemia. Blood uric acid was 4.9 mg. per cent. Serum proteins measured 4.8 Gm. per cent, and the ratio was 0.73/1. The urea clearance was 35 per cent of normal. The phenol-sulfonphthalein test gave no excretion of the dye in fifteen minutes, and only 15 per cent excretion in one hour. Nonhemolytic *B. coli* was cultured from the catheterized urine.

Hospital Course.—The patient was placed on absolute bed rest; the diet was high in protein and salt poor. The patient's only complaint was headache. Blood pressure remained at 180 systolic, and diastolic varied from 100 to 130. The peripheral edema persisted, and the urinary findings continued as on admission. The advisability of termination of pregnancy was concurred in by the Medical Service. On Dec. 4, 1944, the patient was delivered by anterior vaginal hysterotomy under sodium pentothal anesthesia. The uterine contents consisted of a macerated fetus (circa four months), and a placenta which grossly showed a considerable amount of hydatidiform degeneration. Because of brisk bleeding which occurred during evacuation of the uterus, a marked drop in blood pressure took place. The surgical shock promptly responded to the administration of one liter of whole citrated blood. The patient's condition one hour after operation was quite satisfactory, and the blood pressure was 160/118. The postoperative course was quite striking: blood pressure fell to 124/84 by the second postoperative day, and henceforth during the hospital stay the pressure never rose above 120/80. Moreover, the urine promptly cleared of albumin, which varied from only a trace to none from the fourth day on. The urinary sediment continued to show some casts and a variable number of red and white cells. On two occasions the urea clearance was determined, and found to be 25 per cent of normal. The plasma proteins had risen to 7 Gm. per cent by the tenth day following operation. The only postoperative complication was endometritis, which appeared on the second postoperative day when the temperature rose to 40° C. Penicillin therapy was instituted for three days, by which time the patient was clinically well. From the eighth to the eighteenth postoperative day, when the patient was discharged, the convalescence was quite afebrile and uncomplicated.

Pathologic Diagnosis.—Hydatidiform mole. Macerated fetus (circa fourteen weeks) with defect in skull. Sections of the placenta show many chorionic villi which vary considerably in size. Many are exceedingly large. Many villi contain no blood vessels. There is marked proliferation of the trophoblast layers.

Follow-up.—Observations in the Out-Patient Department subsequent to discharge from hospital have revealed no abnormalities on general physical or gynecologic examination. The blood pressure has remained within normal limits; the urine has been free of albumin; and the urinary sediment has been negative. There has been no clinical or laboratory evidence of chorionepithelioma.

Comment

The usual clues to hydatidiform mole include: (1) history of irregular vaginal bleeding during the early months of pregnancy; (2) unduly great enlargement of the corpus uteri for the duration of amenorrhea; and (3) expulsion of the typical vesicular material (which, of course, is diagnostic). A

perusal of the literature, however, would indicate that perhaps not enough emphasis has been placed upon signs of toxemia early in pregnancy as a clue to hydatidiform molar degeneration. That such can be the case has been amply demonstrated both in the instance reported above and in sporadic accounts in the obstetric literature. The syndrome of hypertension, edema, and albuminuria occurring early in gestation should suggest chorionic disease. The onset of the toxic state is more fulminating in instances of hydatidiform mole than in patients suffering with nephritic disease aggravated by pregnancy. Prompt recovery may be anticipated following evacuation of the uterus, if hydatidiform mole is the underlying pathologic entity. Anterior vaginal hysterotomy is a satisfactory procedure for emptying the uterus in such instances. Because of the brisk bleeding which often follows evacuation of molar material, compatible whole citrated blood should be in readiness. When the outcome is fatal following hysterotomy for molar disease, hemorrhage or infection is the usual cause of death. The mortality rate may be reduced by the judicious use of whole fresh citrated blood and/or penicillin.

Elevation of serum chorionic gonadotrophin in eclamptic toxemia has been demonstrated by George and Olive Smith.⁵ Zondek⁶ has amply established the pathologic rise in gonadotropic levels in chorionic disease. Consideration of the aforementioned observations is provocative of speculation concerning the etiology of the toxic states in instances of vesicular degeneration.

Extended follow-up survey is required in instances of hydatidiform mole complicated by toxemia. Follow-up should include: (1) periodic physical examination and quantitative tests for chorionic gonadotrophin, because of the hazard of subsequent chorionepithelioma; and (2) periodic medical evaluation of renal status.

Summary

An instance of severe fulminating pre-eclampsia complicating hydatidiform mole is reported. Immediate and complete recovery followed evacuation of the uterus by anterior vaginal hysterotomy. Toxic states in early pregnancy are a clue to chorionic disease.

The author wishes to express his thanks to Dr. W. R. Barney for his encouragement and advice.

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490 POST STREET

MESONEPHROMA OF THE FALLOPIAN TUBE

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IN 1939 Schiller¹ reported a group of ovarian tumors which he considered as derivatives of mesonephric rests, and suggested the name mesonephroma. Other investigators have differed considerably on the question of histogenesis as postulated by Schiller; however, all agree that such tumors deserve a separate classification.

The gross and microscopic patterns with variations have been described adequately by Jones and Jones² and Stromme and Traut.³

The tumor herein reported was found within the wall of a Fallopian tube and is probably wolffian in origin.

Case Report

The patient, a 32-year-old woman, reported to the outpatient department in September, 1944, complaining of lower abdominal pain. Premenstrual tension, dysmenorrhea, and hypomenorrhea were also evident. Seven months previously she had been examined by two physicians who, discovering a cyst in the right ovary, had advised surgery. Further history revealed that she had consumed large doses of thyroid extract from time to time since 1932. Her weight at this first examination was 195 pounds. The patient had one living child. Two other pregnancies had terminated spontaneously at three and seven months.

Pelvic examination revealed a cyst the size of an orange arising from the right adnexal region. The uterus was enlarged, and a myoma was noted in the anterior wall.

The patient was admitted to the hospital and, on Sept. 15, 1944, laparotomy was performed. At the time of operation a smooth cyst the size of an orange was found replacing the right ovary. The uterus contained intramural myomas. The left ovary appeared quite normal. The right tube presented a nodular appearance and was closed and clubbed at its fimbriated end. In the lateral third of the left tube near the fimbriated end a firm, solid, fusiform tumor measuring 1 cm. in diameter and 2 cm. in length was noted. The serosa overlying the tumor was smooth, and the latter could be moved freely beneath it. Oophorectomy, right, bilateral salpingectomy, and subtotal hysterectomy were performed. The postoperative course was essentially uneventful and, at six months follow-up examination, the patient had no complaints, and pelvic examination revealed nothing of significance.

Pathology.—The unilocular thin-walled ovarian cyst proved to be a simple serous cystadenoma and failed to show any papillary tendencies. The uterus contained intramural and subserous myomas. Chronic salpingitis was observed microscopically in the right Fallopian tube.

The tumor of the left tube was located within the wall of the tube, and a probe was easily inserted the entire length of the tube lumen. The serosa was smooth and could be moved freely over the tumor. On gross section the tumor tissue appeared yellowish-white in color and was solid.

Fig. 1 illustrates the tumor within the tube wall and separated from the lumen of the tube by a wall of fibrous tissue and smooth muscle which also encircles the tumor.

Fig. 2 represents a typical field of tumor tissue with its tubular-like pattern. In some portions of the section tiny cystic areas are noted, lined by a single layer of flattened cuboidal epithelial cells containing vesicular nuclei of moderate size. In other areas these cells are taller and approach a low columnar variety. Hydropic tendencies were noted more frequently toward the periphery of the tumor, and occasionally the bulging nuclei described by Jones and Jones² were demonstrated, as in Fig. 3. Variation in degree of differentiation, as pointed out by Stromme and Traut,³ is clearly noted throughout the sections. Fig. 4 shows that cell height is increased, and in some areas the lining epithelium appears to be multiple



Fig. 1.—Cross section of tube with adjacent tumor.

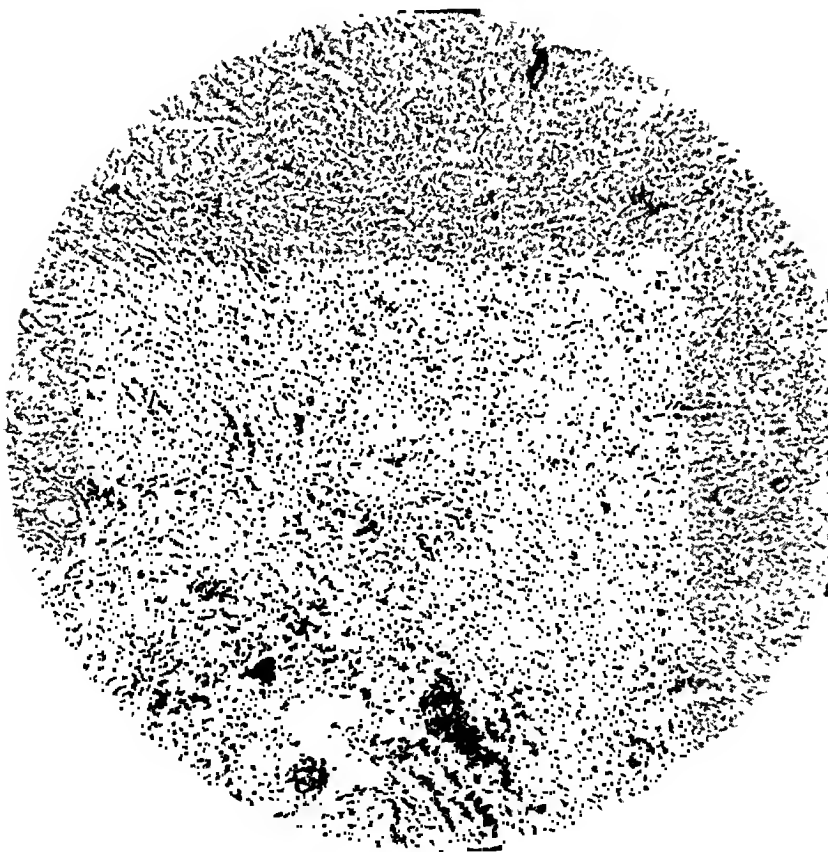


Fig. 2.—Low-power view of tumor tissue showing tubular-like pattern.

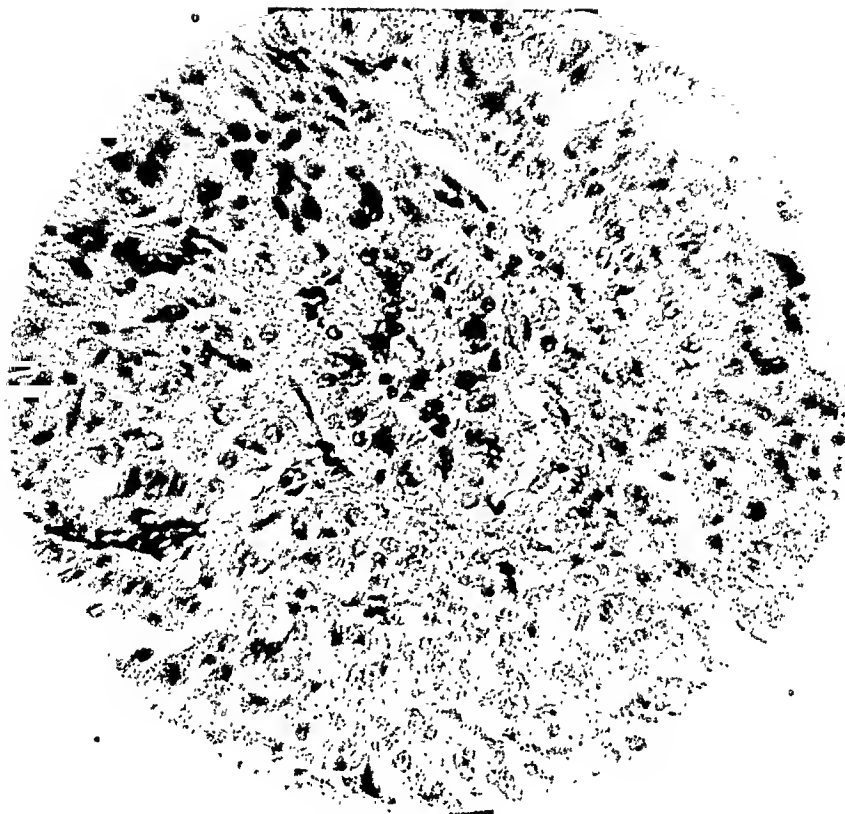
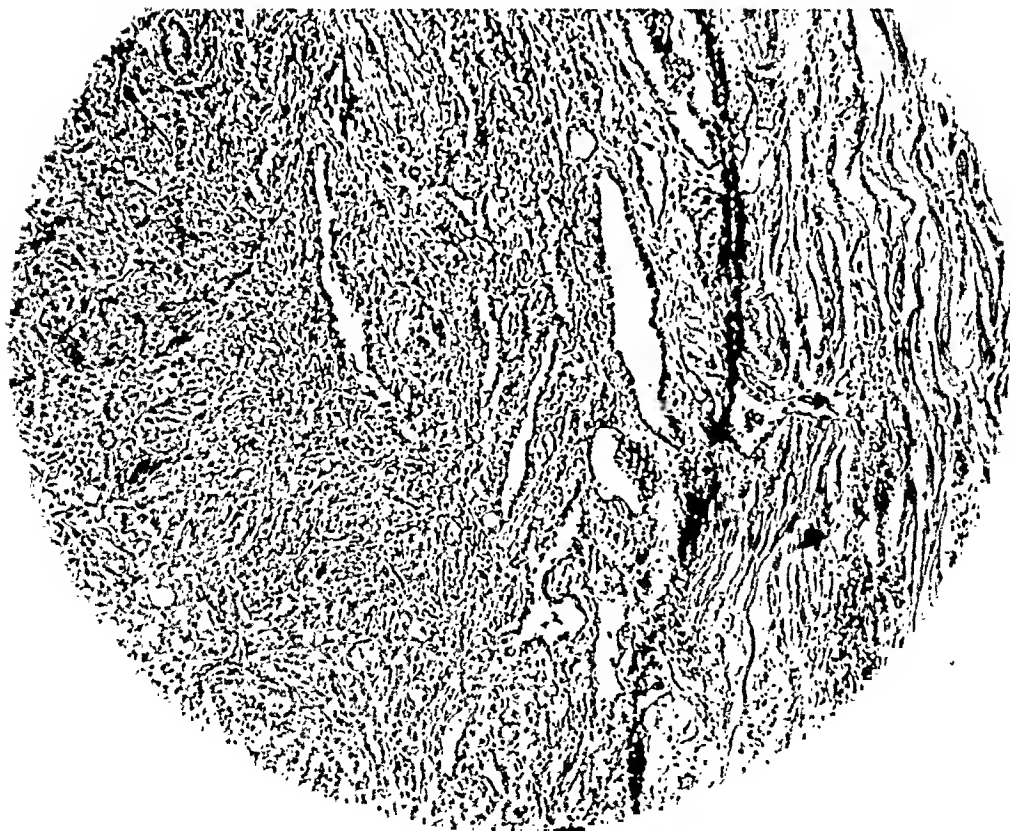


Fig. 3.—Low-power view near margin of tumor showing small cystic spaces lined by flattened cuboidal epithelium with "bulging nuclei."
 Fig. 4.—High-power view illustrating columnar variety of epithelium found in many areas.

in place of the typical single layer. The author failed to notice any structures which resembled glomeruli. Throughout the sections mitotic figures were conspicuously absent.

A report received from the Army Medical Museum,⁴ Washington, D. C., states as follows: "The very interesting lesion of the Fallopian tube showing the adenoma-like structure probably represents a mesonephroma."

Microscopic sections of this tumor were examined by Dr. Emil Novak,⁵ who stated: "I believe the tumor can be called a mesonephroma and that its origin is from mesonephric tubules. It must, however, not be confused with mesonephroma in the Schiller sense."

Dr. G. E. Seegar Jones⁶ also reviewed these sections and offered the diagnosis of mesonephroma. She further indicated that this growth might represent an adenoma or a mesonephric rest, and not an actively growing tumor.

It seems possible, however, that this tumor may represent a very early phase of Schiller's case Number 1.¹

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1305 AMICABLE BUILDING
WACO, TEXAS

OVARIAN PREGNANCY*

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TO DATE there are approximately 85 authenticated cases of true ovarian pregnancy existent. This present case fulfills all the requirements necessary in establishing a diagnosis of ovarian pregnancy as formulated by Spiegelberg.

Case Report

Mrs. F. B., aged 30 years, presented herself for prenatal care on Feb. 21, 1945. She stated that she had her last normal menstrual period on Nov. 30, 1944. On December 15 she experienced cramps and pain in the left lower quadrant accompanied by urinary frequency. She was taken to the hospital on Dec. 16, 1944, and treated for a urinary infection. She was hospitalized for a period of one week. On December 30 a pregnancy test was positive. During the month of January she had vaginal bleeding for a period of 17 days and was informed that this was the beginning of a miscarriage. Pregnancy test done following this episode of bleeding was positive. She bled again vaginally from February 12 to February 17. She was treated as a prenatal case and was examined; the uterus was found to be slightly enlarged, but not equal to the term of gestation. On March 31, 1945, the patient was seized with severe left lower quadrant pain and slight vaginal bleeding, which was extremely dark in color. Pelvic examination at that time revealed a mass in the region of the left adnexa of approximately 8 cm. in diameter. She was then removed to the hospital for surgical intervention of a supposed ectopic pregnancy.

History.—The patient had experienced the onset of menstruation at the age of 12 years. Periods occurred at irregular intervals and lasted two to three days. She had had one pregnancy two and a half years ago with a normal spontaneous delivery. A right salpingo-oophorectomy and appendectomy was done in 1936, a large follicular cyst of the ovary having been removed.

Operation.—With the patient in the Trendelenberg position, the abdomen was opened through a lower midline incision. The left ovary was markedly distended and approximately 8 cm. in diameter, and appeared to be hemorrhagic. There was normal ovarian tissue at the base. The uterus was found to be normal in size and the right adnexa absent. The hemorrhagic area was resected, leaving a small piece of normal ovary. The edges of the small piece of normal ovary were sutured with Pagenstecher linen thread. The abdomen was closed in routine manner.

Pathologic Report.—

Macroscopy: Specimen consisted of an ovary measuring 6.5 by 5.5 by 5.7 cm. On cross section it presented a few cystic areas, and a hemorrhagic, friable appearance.

Microscopy: Section of tissue showed a number of degenerated chorionic villi lined by syncytial cells. Numerous dilated hemorrhagic channels were observed. There was considerable blood clot. A number of deciduous cells were also noted. Small remnants of amniotic membrane were noted within the ovary. The ovarian tissue had been replaced almost in toto by extravasated blood.

*Presented at a meeting of the Philadelphia Obstetrical Society, October 4, 1945.

Comment

Two possibilities as to the mechanism involved in the production of an ovarian pregnancy are to be considered. First, is the fertilization of the ovum in the follicle; and second, is the possibility of fertilization taking place on the surface of the ovary with subsequent imbedding. Since in this case postoperative examination of the ovary revealed the tunica albuginea to have remained intact, we believe the mechanism was that of fertilization of the ovum within the follicle.

136 SOUTH SIXTEENTH STREET

PROLAPSED MALIGNANT TUMOR OF THE BLADDER AS A COMPLICATION OF PREGNANCY

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THE incidence of cancer of any organ and pregnancy is relatively rare, as the two conditions appear in different age groups. Nevertheless, there have been several reports in the literature of carcinoma of the cervix complicating pregnancy, occasionally a case of carcinoma of the rectum, but rarely of tumors of the bladder. Schaetz and Breuncke had one case each of fibromyoma, and Faye one of fibroma of the bladder during pregnancy. Only one case of carcinoma of the bladder has been reported, and that by Wasserr in 1927.

Although there have undoubtedly been other such cases either unrecognized or unreported, this is the only case of a malignant tumor of the bladder which prolapsed from the urethra during pregnancy that has been recorded. We are reporting this case since it is rare, and because the diagnosis of early malignancy during pregnancy can be made only if it is considered as a possibility.

Willson, in a recent article on carcinoma of the cervix in pregnancy, stressed the importance of investigating any bleeding appearing during early pregnancy which persists after one week of bed rest. He felt that prolonged observation of pregnant patients who are bleeding from an undetermined site is more dangerous than a thorough sterile pelvic examination. However, in the details given for his pelvic study, he neglected to mention the importance of first catheterizing the patient, and having the collected specimen examined. The bleeding may possibly be from the bladder, and both patient and doctor believe it to be from the vagina. This mistake is illustrated by the following case.

Case Report

Mrs. G., aged 36 years, gravida iii, para i, had a normal delivery several years previously. Her second pregnancy one year ago was complicated by painless bleeding for several days in the first trimester, followed by a spontaneous abortion. In this pregnancy the same symptoms developed, and bed rest with sedation was prescribed, in the belief that this was another threatened abortion. This form of treatment carried the patient along fairly well until the seventh month of her pregnancy. Then she began to bleed rather profusely and had some lower abdominal cramps. She was advised to go to the hospital.

That evening the bleeding and pains had stopped. She was cross matched, an Rh factor test done, and with suitable blood available, sedation and bed rest was continued. The following morning the bleeding began again, and a large piece of tissue was noted filling the vaginal orifice by one of the house staff, who described it as grossly resembling placental tissue.

At this time the patient was taken to the delivery room and a sterile examination under gas anesthesia was done. The tissue mass was about 4 by 3 by 2 cm., and was at first thought to be an organized blood clot, or possibly placental tissue. However, vaginal examination revealed the vagina and cervix to be clear, and the tissue was found to be on a pedicle which extended up into the bladder. The urethra had been so dilated in passing the tumor that the index finger could easily pass along the pedicle, up the urethra into the bladder.

A urologist was called to see the patient, and he cystoscoped her the following day under pentothal anesthesia. The tumor mass and pedicle were first re-

moved by the electrocautery. The cystoscopic examination then revealed the base of the pedicle to be located slightly superior and lateral to the right ureteral orifice. There was also an annular tumor of the bladder surrounding the outlet (from seven o'clock to two o'clock) which was treated by electrocoagulation. The urologist stated that the tumor was malignant from its gross appearance. The microscopic examination showed a hemorrhagic mass undergoing degeneration. An occasional area was seen with a few cells clustered together, suggesting tumor cells from the bladder mucosa. These areas were so small that it was not possible to make a definite diagnosis, but it seemed that the tissue was from a degenerated portion of a malignant growth.

Her temperature rose to 103° F. on the next two days, but was within normal limits thereafter. The patient was kept in bed, and ten days later spontaneously delivered a normal premature female baby which survived. Two days after delivery deep x-ray therapy was started. She was given sixteen treatments in all, eight treatments daily and then eight every other day, each consisted of 300 roentgen units, all given over the bladder region, both front and back.

Two months later the patient was cystoscoped again and a small recurrence of a portion of the annular tumor was found. This was treated by electrocoagulation. She has not had any further bleeding since her first cystoscopic examination and is to be checked at regular intervals in the future.

Summary

1. A malignant bladder tumor which prolapsed during pregnancy is reported. No other similar case has been found in the literature.

2. Bleeding in early pregnancy that persists over one week should be thoroughly investigated.

References

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1726 EYE STREET

Department of Reviews and Abstracts

Selected Abstracts

Gynecology

Coors, G. A.: Calcification of the Ovaries, *Am. J. Surg.* 56: 492, 1942.

According to the author, a review of the literature on calcification of the ovaries revealed only nine cases reported up to 1930, most of which involved a single ovary. He now adds a tenth case in which both ovaries were calcified. It occurred in a 38-year-old, obese, white woman who had been amenorrheic for nine months, and in whom two stony hard pelvic masses could be felt on vaginal examination, which proved to be calcific deposits by x-ray. At operation both ovaries were removed. They weighed 87 Gm. and 96 Gm., respectively, and their over-all dimensions were $7\frac{1}{2}$ by 4 by 3 cm. Little normal ovarian tissue was present. Postoperative investigation of calcium metabolism in the patient failed to demonstrate any abnormality.

FRANK SPIELMAN.

Seaman, James A.: The Importance of Endocervicitis in Urological Tract Infections, *Southern M. J.* 38: 398, 1945.

Urinary symptoms associated with pyuria are a common complaint in women. Treatment directed exclusively toward the urinary tract frequently results in failure. The two common complaints of cystitis and recurrent pyelitis often may be found with chronic cervicitis. The severe types of pyelonephritis and pyonephrosis are rarely pathologic conditions. They either occur over a period of several years or are most often the result of repeated infections from the same cause.

A case report is presented in which a chronic urinary tract infection was shown to be the direct result of colon bacillus infection from an infection of the cervix.

The treatment is deep electrocoagulation of the cervix. Conization is even better because it completely destroys the infection in the cervical gland.

WILLIAM BICKERS.

Del Castillo, Enrique G.: Treatment of Irregular Functional Uterine Hemorrhages, *Bol. Soc. chilena de obst. y ginec.* 9: 132, 1944.

The author states that the etiology of the disorder is still unknown.

Biopsy of the endometrium is indispensable for the diagnosis and must be done whenever possible. No therapeutic procedure has been found as yet which regulates ovarian function.

There are many methods to stop hemorrhage, even some nonspecific ones. This is illustrated by the success of many different forms of glandular therapy which could be considered as ridiculous but which act through protein shock.

The gonadotrophins, alone or combined, have had their ups and downs, but have provided no proof of their efficacy. Progesterone and progestogens have no major indication. Androgens exert a therapeutic action and should be utilized (testosterone propionate and

dipropionate subcutaneously or preferably intramuscularly; methyl testosterone orally). Thyroid extract, an old and unjustly forgotten medication, now enjoys a well-deserved vogue; its best indication is in young patients. Natural or synthetic estrogens, given by any route, are nearly always effective in stopping hemorrhage. Severe and repeated hemorrhages respond to large doses of estrogens. Irradiation, curettage, and hysterectomy have limited indications.

J. P. GREENHILL.

Arenas, Normando, and Blanchard, Oscar: Experience With Local Sulfonamide Therapy in Gynecology, *An. d. Inst. matern. y asist social, Buenos Aires* 5: 100, 1943.

The authors applied sulfapyridine in powder form or in solution, or a 5 per cent solution of sulfonamide-chrysoidine containing 80 per cent lactose, directly into the uterine cavity in the form of powder or instillation in various gynecologic conditions, such as incomplete or infected abortion, curettage, excision of polyps and of pediculated submucous myomas, with satisfactory results. Mastitis, cracks of the nipples, etc., were likewise successfully treated with local sulfonamide therapy. In general, it was observed that the drugs, by combating infection, have indirectly promoted granulation and cicatrization. Application of sulfapyridine or sulfanilamide to the peritoneum following operations for infectious conditions (pyosalpinx, adnexitis) and especially such operations as total hysterectomy for cervical cancer resulted in an excellent postoperative course and prevented complications.

J. P. GREENHILL.

Gynecologic Operations

Ingersoll, Francis M., and Meigs, Joe V.: The Treatment of Ureters Injured During Gynecologic Operations, *New England J. Med.* 232: 335, 1945.

Accidental injury of a ureter is the most frequent serious complication of gynecologic pelvic operations. The authors report seven urethral injuries in 590 total hysterectomies and one urethral injury in 170 supravaginal hysterectomies done during a five-year period at the Massachusetts General Hospital. These eight cases are used to illustrate the type of injuries that occur and the surgical principles and procedures to be followed in repairing them.

The following conclusions are drawn: immediate recognition of the injury is essential; kidney function should be preserved whenever possible; all urethral anastomoses should be done end to end over a urethral catheter; bilateral ligation is best treated by bilateral nephrostomies; and ureterovaginal fistulas that do not close spontaneously should be repaired either by urethral transplant to the bladder or by nephrectomy.

JAMES P. MARR.

Dannreuther, W. T.: Vaginal Hysterectomy With Pryor Clamps, *Am. J. Surg.* 56: 404, 1942.

In a plea for the retention of the clamp method of performing vaginal hysterectomy in our surgical armamentarium, the author calls particular attention to its value in the very old and/or debilitated patient. In his experience the operation averaged about six minutes, and complications were negligible. As advantages in its use, he lists rapidity of procedure, conservation of the patient's vital resistance, complete absence of shock, safeguarding of bladder and ureters, freedom from postoperative complications, and smooth convalescence. As disadvantages there are undesirability of attempting the operation unless the uterus is mobile, transitory vaginal discharge, possibility of late slight postoperative bleeding, unusually long period of hospitalization, preclusion of doing coincidental plastic operations, and the necessity for special instruments. The technique of the operation using Pryor clamps is described.

FRANK SPIELMAN.

Labor: Management, Complications, Etc.

Sadowsky, A.: The Diagnosis of Uterine Rupture, *Am. J. Surg.* 55: 544, 1942.

During the ten-year period from 1929 to 1938 at the Hadassah University Hospital, Jerusalem, there were thirteen cases of uterine rupture in 9,079 deliveries, an incidence of 0.14 per cent. All of the cases were in multiparas. The maternal mortality was 46.1 per cent, and the fetal mortality, 100 per cent. Although the importance of early diagnosis and operation is stressed in the textbooks, the author points out the difficulties encountered in diagnosis especially where the rupture is not extensive or where it is incidental to delivery from below. In this series only four patients presented the typical picture of uterine rupture as described by Bundle. Operation (hysterectomy) was performed in eleven cases, one patient died before operation, and in the remaining case a diagnosis of incomplete rupture was made twenty-four hours after delivery. The patient recovered without operation. The prognosis, in the author's opinion, is much improved when laparotomy is not preceded by any obstetric (vaginal) intervention, but unfortunately this is often unavoidable.

FRANK SPIELMAN.

Jahier: Hysterectomy Without Preliminary Evacuation of the Fetus, *Bull. Soc. gynéc. et d'obst.* 28: 572, 1939.

The author reports a series of 17 cases of removal of the uterus together with the fetus. There was only one death in the group. These women were operated on in Algeria where serious dystocia is common and amniotic infection is prevalent. The author claims the results of removing the intact uterus with the fetus in such cases are better than the results obtained by cesarean section followed by hysterectomy. He describes his technique in detail. At the end of the operation he uses a Mikulicz drain.

J. P. GREENHILL.

Greig, D. S.: The Uncomplicated Primigravid Breech, *J. Obst. & Gynaec. Brit. Emp.* 52: 122, 1945.

The author quotes a choice of three methods for delivery of an uncomplicated primigravid breech: (1) cesarean section, (2) breech extraction with full anesthesia, and (3) spontaneous delivery with minimal manual aid. In sixty cases delivered by the author, breech extraction was performed only five times. All of the other patients had minimal and very late manual aid. The author finds the following factors important: (1) preparation of the patient, (2) perineal and pudendal nerve block, and (3) preparation of vulva and perineum by "ironing out." This is followed by posterolateral episiotomy, (4) the Lovset technique of delivery of arms, and (5) a short rest in the Burns-Marshall position. The author warns against haste in breech deliveries. Careful deliberate planning of the delivery is essential to a successful result. Waiting patiently for spontaneous delivery and interfering as little as possible is most important. The author had one stillbirth in this series, one case of cerebral irritation that recovered, and one case of fractured left clavicle. This was associated with an Erb's palsy which cleared in one week.

WILLIAM BERMAN.

Menstruation, Dysmenorrhea

Palmer and Orsoni: The Pathogenesis of the Intermenstrual Hemorrhage, *Bull. Soc. gynéc. et d'obst.* 28: 613, 1939-40.

The authors disagree with Beclère, Armelin, and Demange, who claim that chronic infections of the genitals are responsible for intermenstrual bleeding. In their own series of twenty cases they found evidences of infection in only seven cases. In six other cases

small noninfectious lesions were observed and in the remaining seven cases no lesion of any kind was found. In five cases the authors suspected hyperestrinism as the cause and they think the neurovegetative state may play a role.

J. P. GREENHILL.

Beclère, C., Armelin, G., and Demange, R.: Cyclic Intermenstrual Hemorrhage, *Bull. Soc. gynéc. et d'obst.* 28: 568, 1939.

From a study of twenty cases of cyclic intermenstrual bleeding, the authors conclude that the etiology in these cases is a chronic infection of the genitals. The illness is nearly always acquired and appears in young women. In most cases the bleeding is accompanied by lesions of the Fallopian tubes of an infectious nature as evidenced by hysterosalpinography. In 30 per cent of the cases, a latent hydrosalpinx was found. Tests for gonorrhea are frequently positive. In half the cases severe pain is present. The bleeding is produced by a disturbance in ovulation as the result of a chronic genital infection. The best treatment is anti-infectious by diathermy, coagulation, and the sulfonamides.

J. P. GREENHILL.

Pecorone, Rodolfo: Changes of the Menstrual Function in Thyroid Pathology, *Bol. Soc. de obst. y ginec. de Buenos Aires* 23: 491, 1944.

The author has studied 137 cases, including 62 simple goiters (14 diffuse, 7 diffuse nodular, and 40 nodular), 61 Basedow's disease (19 slight, 25 average, and 14 grave), and 8 toxic adenomas.

Menstrual changes were found in 20.3 per cent of the cases of simple goiter. Hypomenorrhea was the most constant observation. Amenorrhea was never found. All disturbances occurred in diffuse nodular or in nodular goiter; they did not initiate the symptomatology, and there was no relation between their appearance and the time of evolution of the goiter. Surgical treatment had a favorable effect on the menstrual function in 18.6 per cent of the cases, an unfavorable effect in 9.3 per cent, and no effect in 72 per cent.

Menstrual changes were found in 63.7 per cent of the cases of Basedow's disease. Hypomenorrhea and amenorrhea were the most constant findings. The frequency and not the intensity of the disturbances was in direct relation to the degree of thyrotoxicosis. Amenorrhea occurred in 22.4 per cent of the cases, was of short duration, and rarely the initial symptom in the general symptomatology of Basedow's disease. Surgical treatment acted favorably on all the characteristics of the menstrual function in 55 per cent of the cases, unfavorably in 17.5 per cent, variably in 5 per cent, and had no effect in 22.5 per cent.

The two phases of toxic adenoma showed similar effects on menstruation as those observed in simple goiter and in Basedow's disease, respectively. Surgical treatment had usually a favorable effect on the menstrual function.

In 11 cases of postoperative hypothyroidism, which was always slight and usually transitory, menstruation was mostly unchanged or showed slight and varying disturbances.

J. P. GREENHILL.

Freed, S. Charles: The Treatment of Premenstrual Distress, With Special Consideration of the Androgens, *J. A. M. A.* 127: 377, 1945.

The author reports the treatment of 60 cases of premenstrual tension or distress in his private practice. The symptoms varied from mild to severe. Thirty of the patients received injections of testosterone propionate on the tenth and third days preceding the menses. The dosage varied from 10 to 25 mg. with each injection. Most of the patients received some relief from this therapy. Outside of an occasionally delayed menstrual period, there were no untoward symptoms. In the second group of 30 women the oral androgen, methyl testosterone, was administered in doses of 10 mg. daily starting 10 to 7 days before the expected period. The author feels that the results were more gratifying

with the oral therapy. The theories of causation are mentioned. He states three chief methods of combating this condition: (1) progesterone and androgen permitting the neutralization of estrogen; (2) vitamin B₁, permitting the normal destruction of estrogen; and (3) ammonium chloride, reducing the sodium retention produced by estrogen.

WILLIAM BERMAN.

Miscellaneous

Courrier, R.: Desoxycorticosterone Is Capable of Maintaining Pregnancy or of Inducing Abortion, *Ann. d'Endocrinologie* 1: 533, 1939-40.

Experiments performed by Courrier on rabbits proved that desoxycorticosterone can prevent abortion in the absence of a corpus luteum and, on the other hand, it may bring about interruption of gestation. When 20 to 30 mg. of desoxycorticosterone acetate were given daily to castrated pregnant rabbits, pregnancy was maintained in the absence of the ovaries, the fetuses grew regularly, and their number was normal. It required about 5 mg. of progesterone daily to produce the same result. It was also shown that not only progesterone but also pregnenolone given orally could accomplish the same thing.

When 20 mg. of desoxycorticosterone acetate was administered daily for six days to pregnant rabbits with intact ovaries and the animals were examined twelve days later, it was found that the gestation had been interrupted. In these cases the desoxycorticosterone either affected the corpus luteum directly or indirectly through the pituitary gland.

J. P. GREENHILL.

Pou Orfila, J.: The Synthetic Concept in Modern Gynecology and Its Practical Importance, *Obst. y ginec. latino-am.* 2: 663, 1944.

The author makes a strong plea not only for the unification of obstetrics and gynecology as one specialty, but also he presents numerous reasons for designating both obstetrics and diseases of women under the one word "Gynecology." The word gynecologist should replace the term obstetrician, man-midwife, etc. In each clinic, hospital, and medical school there can be a chief of obstetrics and one of gynecology, but above both should be an individual who is an authority in both specialties. As the author points out, in Europe the word gynecology is generally used to designate what we in this country separate into obstetrics and gynecology. He therefore makes a plea that synthetic textbooks be written. These should include a section on "General Gynecology" which would deal with data common to both subjects, and the rest of the book should be divided into "Obstetric Gynecology" (or Obstetrics) and "Nongravidic Gynecology."

J. P. GREENHILL.

Newborn

Preston, Mary I.: Late Behavioral Aspects Found in Cases of Prenatal, Natal, and Postnatal Anoxia, *J. Pediat.* 26: 353, 1945.

The author has made a most complete study of 132 patients in which anoxia of varying degrees had occurred either before, during, or after delivery.

In these children the late behavioral aspects were found to fall into two broad divisions: the one with the lesser degree of anoxia taking the form of abnormal hyperactivity combined with hyperexcitability, and the other, which followed a greater degree of anoxia, exhibiting a degree of apathetic behavior incompatible with normal living, strain adding to this the liability of loss of nervous and emotional control.

The anoxia left the intelligence of 97, or 74 per cent, within the normal range, though nullifying its normal use. Anoxia apparently accounted for the subnormal mentality of 35, or 26 per cent, of which 19 were morons, 14 were imbeciles, and 2 were idiots.

The author discusses the possible etiology in the neonatal and postnatal periods. Three babies of anemic mothers suffered from severe cardiac conditions with periods of decompensation throughout pregnancy, caused an oxygen deficiency in the placental circulation—another had excessive oxytoxics and analgesia at birth and did not cry for ten minutes (I.Q. 58).

In the postnatal period, infections and epilepsy probably accounted for the oxygen deficiency and later mental retardation.

Arrest of physical, mental, nervous and emotional, as well as personality development took place throughout the series.

The author is of the opinion that babies delivered under varying degrees of anoxia cannot be pronounced normal until sufficient time has elapsed for the damage done to the nervous system, undeveloped and unmyelinated at the time of the anoxia is disolved, and the sequences of the normal growth processes shows no interference in the unfolding of one maturational mechanism after another as expressed by normal functioning in the first few years of life.

JAMES P. MARR.

Hogg, Paul, and Bradley, Chester D.: *Pneumococcus Meningitis in the Newborn*, J. Pediat. 26: 406, 1945.

A review of the literature by these authors described only twenty-eight cases of this disease occurring in the first two weeks of life. All were fatal except three, the last being the authors' case which was treated with sulfadiazine.

JAMES P. MARR.

Glaser, Kurt, and Simpson, M. Markson: *The Value of Serum Protein Determinations in Cases of Suspect Erythrodermia Desquamativa of the Newborn*, J. Pediat. 26: 367, 1945.

The authors present a case report of an infant with a skin condition best classified as erythrodermia desquamativa, with a fatal result. From this study it can be concluded that every case of so-called "infantile eczema" of prolonged duration and without the usual regressions might be considered as potential erythrodermia desquamativa and the serum protein level should be determined. This determination will not only help in the prognosis of cases, but also indicate early treatment to replenish the blood stream and thus the liver cells with the necessary protein, before a severe parenchymatous injury to the liver occurs. Local treatment of the skin seems of little value.

JAMES P. MARR.

Item

American Board of Obstetrics and Gynecology, Inc.

The following diplomate has been certified and is added to the previously published list: Dr. Charles S. Fine, Oakland Regional Hospital, Oakland, California.

Erratum

In the article entitled "The Fetal Mortality in Women During the Prediabetic Period" by Joseph Herzstein, M.D., and Henry Dolger, M.D., New York, N. Y., which appeared in the March, 1946, issue of the JOURNAL, the sentence appearing on the fifth line from the bottom on page 420 should read: "In a control group of 398 infants born to nondiabetic women comparable in age to *their* diabetic patients, *the* fatality rate was 3.01 per cent."

Announcement

With the present issue of the JOURNAL, the former size is resumed. It is to be hoped that no further restrictions in the number of pages and the quality of paper will be imposed.

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